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HYPERTENSION AND CARDIAC RUPTURE

A CLINICAL AND PATHOLOGIC STUDY OF SEVENTY-TWO CASES, IN THIRTEEN OF WHICH RUPTURE OF THE INTERVENTRICULAR SEPTUM OCCURRED

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THE literature on cardiac rupture is replete with names great in medical history. The condition was first described by William Harvey,[1] in 1647. By 1765, Morgagni[2] was able to collect autopsy records of ten patients who had died from this cause, and added one that he had observed. Morand,[3] Blaud,[4] Cruveilhier,[5] Adams,[6] Hodgson,[7] and Barth[8] also made contributions to this subject.

Benson, Hunter, and Manlove,[9] in 1933, reviewed the subject and traced clearly the evolution of our knowledge of spontaneous rupture of the heart. These authors divided the accumulation of our present knowledge of this subject into three periods. In the first period, previous to 1861, the authors[1-8] failed to observe that coronary sclerosis and thrombosis, with consequent myocardial infarction, were the common underlying causes of rupture. The areas of infarction through which rupture occurred were undoubtedly noted but were regarded as areas of fatty degeneration. Malmsten[10] recorded, in 1861, his observations of a ruptured heart in which he described an area of softening and rupture caused by an old thrombus in the anterior descending coronary artery. After this, many others made similar observations. The second period ended in 1896 with a review by René Marie,[11] who correctly stressed the relationship of coronary sclerosis and thrombosis to myocardial infarction and rupture.

We are at the present time in the third period, during which some progress has been made in the study of the coronary arteries, their collateral circulation, and the usual sites of thrombosis (Blumgart, Schlesinger, et al.[12, 13, 14]). Many cases of interventricular rupture have been reported, together with criteria for the clinical diagnosis. Among

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the factors considered in cardiac rupture, softening of the myocardium after coronary thrombosis has received the greatest emphasis. Little discussion has been given to the bursting power of the intraventricular pressure, although it seems to have been considered necessary. Krumbhaar and Crowell[15] mention that a rise in blood pressure during sleep, as demonstrated by MacWilliam,[16] may be the exciting cause of rupture. Beresford and Earl[17] add that a rise in blood pressure during defecation may precipitate rupture. The possible role of arterial hypertension after infarction is mentioned only by Mallory, White, and Salcedo-Salgar,[18] who make the following statement: "Another factor of importance in this connection is the intraventricular pressure. The higher this pressure, the more likely rupture is to occur." In their study of the speed of healing of myocardial infarction in seventy-two patients there were eight instances of rupture. In two of the eight, hypertension was present after infarction had occurred. These authors also say that the enzymatic action of polynuclear leucocytes in the area of necrosis may tend to reduce its resistance.

Since only a small percentage of infarcts undergo rupture, the factors that contribute to the mechanism deserve special consideration. Among these may be age, sex, increase of subepicardial fat, opposing pull of muscle bundles, and hemorrhage into the area of infarction.

The present study, which was started in 1934, was undertaken because it seemed to us from our autopsy experience that rupture often followed the first attack of coronary thrombosis in persons who had hypertension and some degree of cardiac hypertrophy, and whose hypertension persisted after infarction. In most of these hearts there appeared to be a sufficient amount of undamaged myocardium outside the area of infarction to maintain a relatively high intraventricular pressure. We have attempted by a study of available material to find out whether or not a correlation exists between blood pressure and rupture. In addition, we have considered the possible relationship of scarring of the myocardium and heart weight to rupture.

MATERIAL

This study is based upon the records of all patients who were found to have rupture after myocardial infarction caused by coronary disease in a series of 25,000 consecutive autopsies which were performed at the Los Angeles County Hospital from July, 5, 1924, to August 15, 1941. All instances of recent, unhealed infarction, without rupture, among these autopsies, were used as a control group.

A study was also made of the records of 100 patients who had convincing clinical and electrocardiographic evidence of acute myocardial infarction and recovered sufficiently to leave the hospital. These records were taken in consecutive order from the files of our department of electrocardiography.

STATISTICAL SURVEY

Among the 25,000 autopsies, 865 (3.4 per cent) hearts were found to have one or more unhealed infarcts. Among the 865 there were 72 (8.3 per cent) that had ruptured (0.29 per cent of the total number of autopsies). The rupture of the myocardium was in an area of recent infarction in each instance. In the group of 72 ruptured hearts, only 19 (26.3 per cent) contained scars, whereas there were scars in 58.4 per cent of the unruptured hearts with unhealed infarcts.

The age incidence by decades of those who had infarction alone, as compared with those who had rupture, is shown in Fig. 1. The high incidence of rupture in the seventh and eighth decades closely parallels the incidence of infarction in these decades. The difference shown in the eighth decade is not statistically significant. There was no significant difference in age incidence between those with and those without myocardial scars.

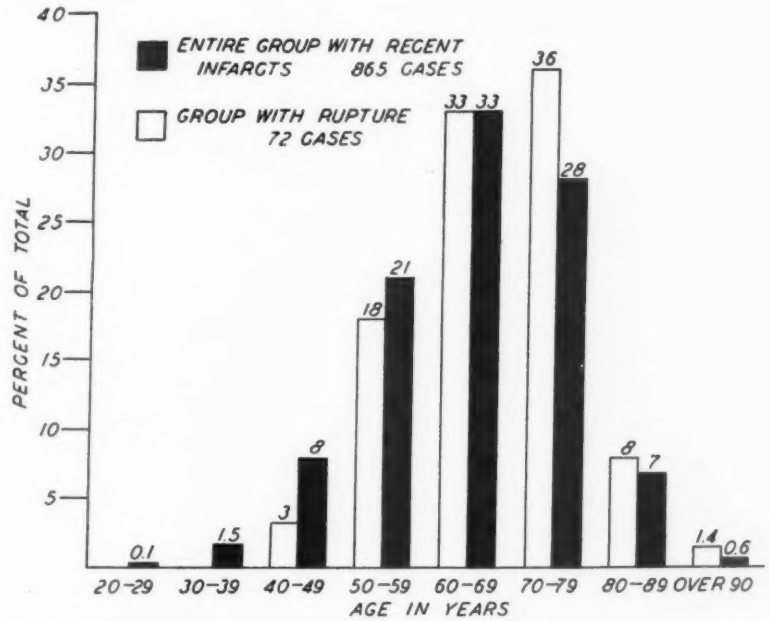

Fig. 1.—Age distribution of cardiac rupture, compared with that of fatal myocardial infarction.

Of the 865 patients who had one or more unhealed myocardial infarcts, 601 (69.4 per cent) were males. Of the 72 whose hearts ruptured, only 40 (55.5 per cent) were males. This difference is statistically suggestive.

The seasonal variation of incidence of rupture of the heart did not differ significantly from that of myocardial infarction. The frequency of obesity in the group with ruptures was practically the same as that among those who had infarcts that did not rupture.

In the first half of the records studied, covering the period from July, 1924, to November, 1935, there were 266 instances of myocardial infarction with 23 (8.6 per cent) ruptures; but in the second half, 599 instances of infarction and 49 (8.2 per cent) ruptures were observed. Thus it appears that the increased incidence of myocardial rupture is caused by a proportional increase in the number of infarctions of the heart in recent years.

PATHOLOGY

Gross.—A pericardial cavity distended with blood at necropsy has always aroused the interest of pathologists. Some consider it a rare occurrence. By far the most common cause of hemopericardium is myocardial rupture. In the autopsies reported here, the amount of blood in the pericardial cavity was usually estimated by the autopsy surgeon. These estimates varied from 150 to 700 c.c., but the majority were recorded as being from 200 to 250 c.c. Because of the inelastic nature of the parietal pericardium, this volume is probably sufficient to cause tamponade. This differs from chronic disorders, such as tuberculous pericarditis, in which the parietal pericardium has had time to become greatly distended, and, in consequence, a liter or more of fluid may collect in the cavity.

TABLE I

SITE OF RUPTURE	SITE OF CORONARY THROMBOSIS					
	NO.	L.D.	L.C.	NONE SEEN	R.C.	MULTIPLE
Left ventricle, anterior	37	33		3		L.D. & R.C.
Left ventricle, posterior	10	1	3	1	5	
Left ventricle, lateral	5	1	4			
Right ventricle, anterior	3	2				L.D. & L.C.
Right ventricle, posterior	1					L.D. & L.C.
Not recorded	3		1	2		
Interventricular septum	13	5		2	5	L.D. & L.C.
Totals	72	42	8	8	10	4

L. D., Left Descending.
L. C., Left Circumflex.
R. C., Right Coronary.

The sites of rupture, with the corresponding location of thrombosis in the coronary arteries, are seen in Table I. It is of interest that the left anterior descending branch is the artery most often involved (58.3 per cent), and that, after its occlusion, ruptures occurred in all portions of the ventricles and septum except the posterior portion of the right ventricle. In one instance (Autopsy No. 22821), the area of infarction and rupture was in the posterior wall of the left ventricle, whereas the thrombosis occurred in the anterior descending branch of the left coronary. In the group in which interventricular septal rupture occurred, the anterior descending and the right coronary were involved an equal number of times.

Our interest in the relationship of blood pressure to rupture prompted us to study the size of the infarcts. It is logical to assume that the blood pressure after infarction depends to some extent on the proportion

of the uninvolved muscle to the ischemic portion. The size of the infarcts was recorded in 35 ruptured hearts. The dimensions of these varied from 2 x 1 cm. to 11 x 9 cm. In 25 of the 35 specimens the greatest dimension of the area of infarction was 5 cm. or less. In three in which the infarct was 50 sq. cm. or larger, the highest blood pressure recorded after occlusion was 130/90. These figures may be compared with those in a similar group without rupture. The size of the infarcts in 35 unselected instances in which measurements were available varied from 2 x 1 cm. to 10 x 8 cm. Nineteen were 5 cm. or less in their greatest dimension, and, correspondingly, there were more of the larger infarcts. In six the infarct was 50 sq. cm. or larger, and the blood pressure in this group of patients varied from unobtainable to 138/94. In five of these six the blood pressure was normal or subnormal, in spite of the fact that all five hearts were enlarged.

The following case illustrates how early even a small infarct may rupture when the intraventricular pressure is high.

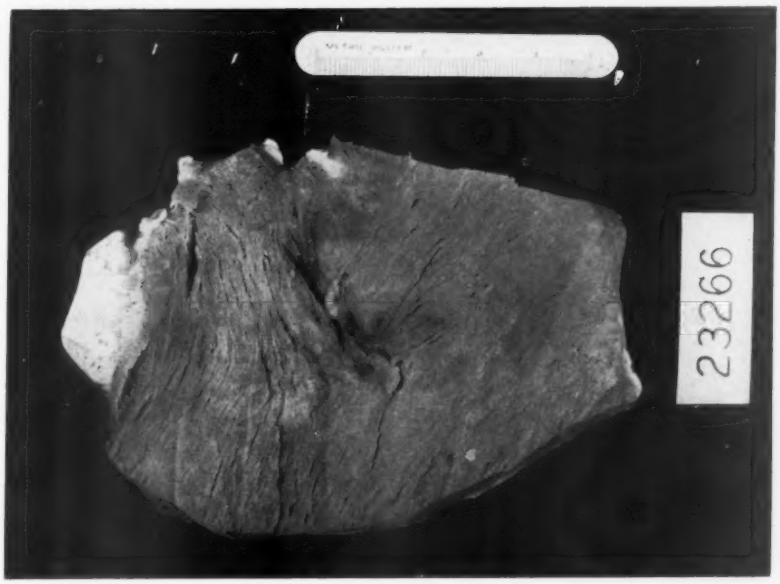

Fig. 2.—Rupture of lateral wall of left ventricle through a small recent infarct. (Aut. No. 23266.)

Autopsy No. 23266, J. I., a white man, aged 76 years, entered the hospital Dec. 2, 1939, because of severe frontal headaches and failure of a recent enucleation wound of the eye to heal. Pyuria and hypertension (190/110) were first discovered in 1938. On entry the temperature was 99° F., the pulse rate, 84, and the respiratory rate, 18. The blood pressure was 210/100. The urine contained albumin (+++). The blood creatinine was 10.4 mg. per hundred cubic centimeters. The patient became irrational, complained once of shortness of breath, and died suddenly twenty-four hours after admission.

The necropsy was performed fourteen hours after death. The essential changes were in the heart and kidneys. The pericardial cavity contained 110 c.c. of blood, the heart weighed 370 grams, and a linear tear was present on the lateral surface

of the left ventricle (Fig. 2). The rupture had occurred through a small infarct, 4 × 2 cm. The coronaries were sclerotic, and a recent thrombus completely occluded the left anterior descending branch. The kidneys were severely scarred; the right weighed 30, and the left, 60 grams. On histologic examination, the renal changes were those of chronic pyelonephritis and extreme atrophy. Microscopic study of the myocardium disclosed only a few areas of early necrosis of muscle fibers (Fig. 3). A few interstitial hemorrhages were present along the course of the rupture. In some areas the tear had apparently occurred through muscle in which there was not yet histologic evidence of necrosis.

We believe that such a rupture, occurring in a small infarct so soon after occlusion of the artery, is best explained by the high blood pressure.

The course of the tear in the myocardium was usually somewhat tortuous, but the records in this regard were incomplete. The length of the tear in the epicardium varied from 0.3 cm. to 3.3 cm.; the average was 1.6 cm. The endocardial tears were smaller and were difficult to measure. Many authors mention their frequency near the base of the anterior papillary muscle. This was mentioned only rarely in our records.

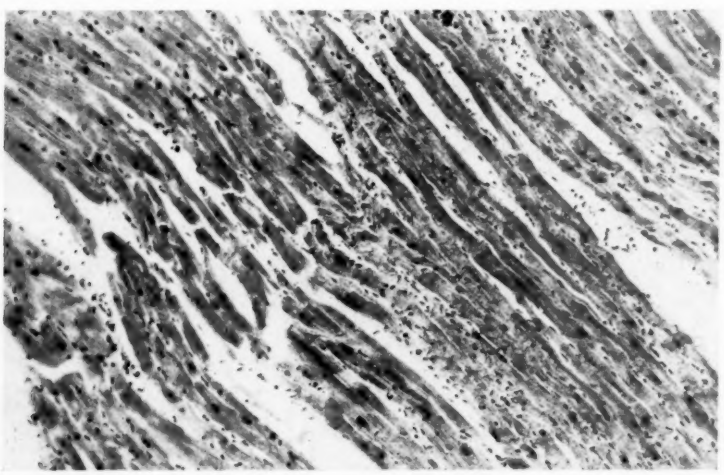

Fig. 3.—Patchy necrosis of myocardium adjacent to rupture seen in Fig. 2 (×105).

Sixty-six of the ruptured hearts were weighed. The average weight was 458.3 grams. Fifty-two (78 per cent) weighed 400 grams or more. We have considered that a cardiac weight of 400 grams or more indicates hypertrophy. The average weight in the control group of 733 infarcted hearts, without rupture, was 488 grams and 594 of these (81 per cent) weighed 400 grams or more.

Scars were seen in 19 hearts, as mentioned above. In 12 the scarring was diffuse in nature; in 7 the scars were circumscribed and were interpreted as indicating old infarcts. In two of these a recent infarct and rupture had occurred in the center of an old infarct. Six of the seven hearts with old infarcts weighed 425 grams or more, and hypertension was present in five of the patients after occlusion.

The thickness of the left ventricle was recorded in 37 cases. The range was from 10 to 25 mm., and the average was 15.4 mm. Twenty-seven were 14 mm. (the borderline for hypertrophy) or more in thickness.

Increase of subepicardial fat has often been mentioned as a predisposing cause of rupture. In these records the amount of fat was rarely mentioned, but in the experience of the authors, which includes 16 of the hearts in this series, an increase of subepicardial fat appears to be associated fairly frequently with cardiac rupture.

No conclusions could be drawn from the descriptions of the size of mural thrombi, because in more than half of the hearts thrombi had not yet formed, or at least they were not mentioned in the protocols.

Microscopic Observations.—Sections of the myocardium were available for histologic study in 41 of the cases of rupture. They were studied from the standpoint of establishing criteria which would differentiate infarction with rupture from other myocardial infarctions. Only two observations of suggestive value were made. In 22 of the 41 hearts there was a complete, smudgy type of necrosis which involved all the tissue over a wide area. The other observation substantiates one made long ago by many students of the problem. This was widespread, heavy infiltration of the area of infarction with polymorphonuclear leucocytes, and it was found in 18 cases. This may resemble an abscess (Bresnihan[19]). It is well known that necrotic polymorphonuclear leucocytes liberate a proteolytic enzyme. This may conceivably add to the softness of an area of infarction.

In comparing these changes with those in the hearts which were infarcted but unruptured, the same type of necrosis and heavy infiltration with polymorphonuclears was seen, but in a smaller proportion of specimens. Undoubtedly the appearance of an infarct will depend on the time that has elapsed since the onset, and, as rupture is likely to occur when the infarct is softest (three to twelve days), the observed changes may be what one should expect to find. However, on gross examination there appears to be a great variation in the degree of softening of infarcts of the myocardium which is not entirely dependent on the time element. In the literature concerning rupture, many authors have mentioned the ease with which the infarcted muscle may be torn with the finger tip. On the contrary, rupture can occur in spotty infarcts and in those in which little softening has occurred (Autopsy No. 23266). Careful gross and histologic study of all infarcts, combined with antemortem blood leucocyte counts, would be helpful in ascertaining the relation of leucocytic infiltration to softening.

Infarction of the endocardium and thrombosis of the Thebesian vessels as further factors in weakening the heart wall were also searched for, but no conclusive evidence was obtained. Rarely did the area of infarction include the endocardium. In the instances in which there was thrombosis of the Thebesian vessels, it was a part of a mural thrombus. The number of instances in which the endocardium was not involved by the necrosis in myocardial infarction was surprising.

A variety of renal changes was observed. Sections of kidney were available in 53 of the group with cardiac rupture. Seven of 47 persons who had cardiac hypertrophy and/or hypertension had kidneys of normal appearance. All the rest had evidence of hypertensive disease. Most common was diffuse arteriolar nephrosclerosis (35 cases). Chronic pyelonephritic, contracted kidneys were present in three. There was one instance of diabetes and intercapillary glomerulosclerosis (Kimmelsteil-Wilson's disease) and one of chronic glomerulonephritis.

CLINICAL DATA

Statistics regarding the available blood pressure measurements in three groups of patients are recorded in Table II. The first is a group of 100 patients who survived and recovered sufficiently to leave the hospital after myocardial infarction had been diagnosed from the clinical and electrocardiographic manifestations. The second group consists of those who had unhealed and unruptured infarcts in their hearts. The blood pressures were taken after infarction. The third is the group with ruptured myocardial infarcts. The blood pressures used were those taken between the time of infarction and rupture.

For uniformity, the following method of tabulating blood pressures was used. When more than one measurement was recorded on the chart, the average was used. The mean blood pressure was used in those instances in which the systolic pressure was above the indicated amount of 140 or 160 and the diastolic was below 90 or 100, and in instances of a higher diastolic and a lower systolic. With the exception of those whose diastolic pressures were below 70 mm. Hg, those with a mean blood pressure of 115 were considered to have a blood pressure of 140/90, and those with a mean pressure of 130 were included as having a blood pressure of 160/100.

TABLE II

	TOTAL	B.P. 140/90 OR ABOVE		B.P. 160/100 OR ABOVE		AVERAGE SYSTOLIC MM. HG.	AVERAGE DIASTOLIC MM. HG.
		NO.	%	NO.	%		
Group I—Nonfatal myocardial infarction	100	23	23	9	9	125	78
Group II—Fatal infarction, unruptured	657	210	32	118	18	128	81
Group III—Fatal infarction, ruptured	62	39	63	20	32	148	93

The greater incidence of hypertension in the group of patients with ruptured hearts is significant, particularly when 140/90 mm. Hg is taken as the hypertensive level. The average blood pressure in this group also is significantly higher.

The data on Groups II and III are arranged in Table III to show the frequency of rupture of the heart when the blood pressure is low and

when it is high. It appears from this tabulation that, in the presence of myocardial infarction, blood pressures above 140/90 are as likely to be associated with rupture of the heart as pressures above 160/100.

TABLE III

	MYOCARDIAL INFARCTION		
	TOTAL	RUPTURED	
		NUMBER	% OF TOTAL
Blood pressure below 140/90	470	23	4.9
Blood pressure 140/90 or above	249	39	15.7
Blood pressure below 160/100	581	40	6.9
Blood pressure 160/100 or above	138	20	14.5

Table IV is designed to ascertain whether there is any correlation between cardiac size and tendency of the infarcted heart to rupture. The notable facts shown are that the proportion of rupture is highest (25 per cent) in the group with small hearts and hypertension, and lowest (4 per cent) in the group with large hearts and low blood pressure.

TABLE IV

	NO RUPTURE (644 CASES)		RUPTURE (58 CASES)		TOTAL	% RUPTURED
	NUMBER	%	NUMBER	%		
Heart weight— 400 Gm. or more B.P. 140/90 or above	187	29	31	53	218	14
B.P. under 140/90	354	55	14	24	368	4
Heart weight— under 400 Gm. B.P. 140/90 or above	21	3	7	12	28	25
B.P. under 140/90	82	13	6	10	88	7

In the records of 66 of the patients with ruptured hearts, sufficient data were present to establish the date of an attack that could be reasonably assumed to be the result of coronary occlusion and infarction of the heart. The interval from infarction to rupture was calculated from this date. The majority of the ruptures (52, or 78.8 per cent) occurred from the third to the twelfth day after infarction, and 98.5 per cent on or before the sixteenth day. Six instances of rupture were thought to have occurred one day after infarction, and one on the twenty-ninth day. The average calculated time from infarction to rupture was 7.4 days.

The records of 16 patients indicated that there was a return or marked increase of pain at the time of the rupture. Only 6 patients were recorded as having exerted themselves at the time of, or shortly preceding, the rupture, and in each instance the exertion was mild. Five patients died during sleep.

Data regarding duration of life after rupture were present in 56 records. In this respect the patients are clearly separated into two groups,

namely, those whose heart wall ruptured into the pericardium, and those whose rupture was of the interventricular septum. Of the former group of 45 patients, it is recorded that 24 died suddenly, 18 died within a few minutes, 2 lived for fifteen minutes, and 1 lived for three hours. Numerous small perforations, rather than a single tear, were noted in the wall of the heart of the last-mentioned patient.

Interventricular Septal Rupture.—It was possible in 11 of the 13 patients who had interventricular septal rupture to ascertain the length of life after the rupture. Ten of these patients lived from nine hours to seven days, with an average survival period of 2.25 days. One patient lived for several months after the rupture (Fig. 4). In 6 cases, blood pressures were taken between the time of infarction and rupture, and after rupture of the interventricular septum. The respective averages were 160/100 and 85/60, an average decrease in pressure of 75 mm. Hg systolic and 40 mm. Hg diastolic. A precordial systolic murmur was observed in 11 of the 13 patients who had rupture of the interventricular septum. In 3 of these patients, all within the last two years, a correct ante-mortem diagnosis was made.

Fig. 4.—Old healed interventricular septal rupture. (Aut. No. 11590.)

COMMENT

Comparison of the incidence of rupture of the heart in various series of autopsies must, of course, take cognizance of the type of patients comprising each series. From an institution which cares predominantly for elderly patients with mental disturbances, Beresford and Earl[17] reported an incidence of 31 ruptures among 2,374 autopsies. This is an

even higher incidence than that reported by Benson, Hunter, and Manlove,[9] who found 27 ruptures among 2,112 coroner's autopsies. Krumbhaar and Crowell,[15] in 1925, reported only 7 ruptured hearts among 16,000 autopsies at the Philadelphia General Hospital. They also quoted Romeik's Munich series of 13,000 autopsies, in which 7 ruptured hearts were found, and a series from Leipzig in which 9 ruptures were present in 8,000 autopsies. The average incidence in these three series was 0.06 per cent. This is much less than the 0.28 per cent of 4,657 autopsies on general hospital and private patients reported by Benson, Hunter, and Manlove,[9] in 1933. The above reports are not limited to rupture of the heart wall through myocardial infarcts, and they do not give the total number of myocardial infarcts in the autopsy series. The relatively great frequency of cardiac rupture in our series (0.29 per cent) bears a certain more or less constant relationship to the incidence of myocardial infarction among patients who die in the Los Angeles County Hospital.

Before making this study we were impressed by the increased number of ruptures of the heart in recent years. This study reveals, however, that it is not the frequency of rupture in infarcted hearts that has increased, but rather the incidence of myocardial infarction. The great increase in frequency of fatal myocardial infarction in the second half of our group is most impressive. In the first 12,500 autopsies there were 266 instances of myocardial infarction. In the second 12,500 autopsies myocardial infarction was present in 599. The explanation is not apparent.

The significantly lower incidence of gross scarring among the ruptured, as compared with the unruptured, hearts in this group has an important bearing on the factors in rupture of a heart wall. Only 1 in 25 of the infarcted hearts which contained scars ruptured, whereas 1 in 6 of the unscarred hearts ruptured. It thus appears that an infarct is about four times as likely to rupture in a heart in which the coronary circulation has previously been adequate. One reason may be that in unscarred hearts the blood pressure after infarction is maintained at a higher level because there is a greater mass of undamaged myocardium. The average blood pressures in these groups, however, do not support this assumption. We believe the most important reason that scarred hearts are less likely to rupture is the fact that collateral circulation is greatly increased in these hearts, so that subsequent areas of infarction may be less likely to be soft and friable. Another reason may be that, in an area of infarction which contains fibrous tissue as a result of previous coronary insufficiency, the fibrous elements may be resistant to ischemia, thus adding support to the necrotic muscle.

Although it must be admitted that blood pressures taken some time before rupture of the heart may not indicate the exact pressure at the time of rupture, we believe that in a fairly large group of patients these blood pressure records are of real significance. The incidence of elevated blood pressure in the group with ruptured infarcts of the heart was

about twice as great as among those who died with unruptured infarcts, and about three times as great as in the group that survived myocardial infarction.

From the data in Table III it appears that the victims of myocardial infarction who die are two or three times as likely to die of a ruptured heart if the blood pressure is high. Only 23 (4.9 per cent) of the 470 patients with blood pressure below 140/90 suffered rupture of the heart, whereas 39 (15.7 per cent) of the 249 patients with blood pressures above this figure suffered rupture of the heart. Practically the same proportions obtain when 160/100 is taken as the lower level of high blood pressure.

It must be remembered that arterial blood pressure is indicative of the function of the left ventricle; therefore, our data regarding blood pressure are hardly applicable to the study of rupture of the right ventricle. The present series of 72 ruptures contains only 4 instances of rupture through the right ventricle.

Tabulation of the blood pressures of those whose hearts weighed less than 400 grams and those whose hearts weighed more than 400 grams (Table IV) reveals that large hearts, with low blood pressure, are least likely to rupture, and that small hearts in patients who have hypertension are most likely to rupture.

A combined study of the gross and microscopic observations on ruptured hearts after coronary thrombosis, plus the evidence obtained from blood pressure readings after infarction, leads us to feel that the chief factors which determine rupture are softening of the infarct and height of intraventricular pressure. Either factor may be predominant. A soft, friable infarct may rupture with normal intraventricular pressure. On the other hand, a small, spotty infarct may rupture when the intraventricular pressure is high. The high incidence of rupture after infarction in mentally defective patients reported by Beresford and Earl[17] may be ascribed to the fact that such patients are less cognizant of pain and therefore exert themselves unduly. It seems reasonable to assume that the height of intraventricular pressure would vary inversely as the size of the infarct. Our data suggest such a correlation, for few hearts with infarcts larger than fifty square centimeters were capable of supporting an elevated blood pressure. The factors which determine the degree of softening of an infarct of the myocardium are complicated, and one's reasoning is beset by unknown factors. The degree of anoxia of the area is a factor of prime importance. This is determined by the extent of the collateral circulation, which may vary greatly. Increased subepicardial fat and fatty infiltration of the muscle tend to increase softness in an area of necrosis. The opposing pull of muscle bundles may increase a tendency to tear. Heavy infiltration of polymorphonuclear leucocytes and subsequent disintegration, necrosis, and liberation of liquefying enzymes may well increase the softness of an infarcted area. The reason for the variation in degree of infiltration with neu-

trophils is an unsolved problem. Rosenbaum and Levine[20] find that the prognosis is poorer in patients who have high leucocyte counts, but do not mention the level in those whose hearts ruptured.

Interventricular Septal Rupture.—The interventricular septum was ruptured in 13 of the 72 hearts. This seems to be a surprisingly large number, in view of the fact that the condition has previously been reported in only 23 patients.[21] Benson, Hunter, and Manlove[9] reported 40 ruptured hearts, but only one was ruptured through the septum. Beresford and Earl[17] reported 46 ruptured hearts, but none was ruptured through the septum. An ante-mortem diagnosis of interventricular septal rupture was reported in 4 of the 23 patients mentioned above. In our group it was made in 3 of the 13 patients. These three correct diagnoses were made during the last two years. The diagnostic significance of a loud precordial systolic murmur which appears suddenly in a person who has recently suffered a coronary occlusion is now well recognized by the attending and resident staffs of this hospital. The clinical course of the patients with rupture of the interventricular septum differed from that of those with other ruptures in that the patients lived longer (nine hours to seven days) after the rupture, and death was, therefore, less sudden and unexpected.

The clinical importance of this study seems obvious. Extra precautionary measures should be taken to keep the patient as quiet as possible between the third and sixteenth days after the first attack of coronary thrombosis. This is especially important when the blood pressure remains above 140/90 mm. Hg.

SUMMARY

1. In a series of 25,000 autopsies at the Los Angeles County Hospital between July, 1924, and August, 1941, there were 865 hearts which contained unhealed infarcts caused by coronary disease.

2. Among these were 72 instances of spontaneous rupture through an area of ventricular infarction; 50 (70 per cent) were on the anterior surface of the heart. In 13 instances the rupture was through the interventricular septum.

3. Scarring was present in 58.4 per cent of the unruptured hearts and in only 26.3 per cent of the ruptured hearts.

4. In the ruptured hearts the infarcts tended to be smaller, more completely necrotic, and more heavily infiltrated with polymorphonuclear leucocytes.

5. Of 100 patients who had nonfatal myocardial infarction, 23 (23 per cent) had a blood pressure of 140/90 or above. The average blood pressure was 125/78.

6. Of 657 patients who had myocardial infarction that terminated fatally without rupture, 210 (32 per cent) had a blood pressure of 140/90 or above. The average was 128/81.

7. In 62 patients who died as a result of cardiac rupture, the blood pressure was 140/90 or above in 39 (63 per cent). The average was 148/93.

8. The average calculated time between infarction and rupture was 7.4 days. Ninety-eight per cent occurred on or before the sixteenth day after infarction. Seventy-eight per cent occurred between the third and twelfth days.

9. Among 368 patients with heart weights of 400 grams or more and a blood pressure of less than 140/90 after infarction, only 4 per cent had cardiac rupture.

10. Rupture of the heart occurred in 25 per cent of the 28 patients whose hearts weighed less than 400 grams and whose blood pressures were 140/90 or above after myocardial infarction.

11. In the first 12,500 autopsies in this series, done between 1924 and 1935, 266 instances of myocardial infarction and 23 (8.6 per cent) ruptures were observed. In the second half, done between 1935 and 1941, myocardial infarcts were present in 599 cases and ruptures in 49 (8.2 per cent).

CONCLUSIONS

The following conclusions regarding spontaneous rupture of the heart through an area of myocardial infarction appear justifiable from our data:

1. The degree of softening of the myocardium and the height of the intraventricular pressure are the determining factors in relation to cardiac rupture.

2. Patients who have hypertension which persists after infarction are three times more likely to develop cardiac rupture than those who have normal or subnormal blood pressures.

3. Hearts of normal weight in patients whose hypertension persists after infarction are most likely to rupture.

4. Hypertrophied hearts in patients who have a normal or low blood pressure after infarction are least likely to rupture.

5. If scarring is present in the myocardium, the likelihood of rupture is only one-fourth as great as in unscarred hearts.

6. Interventricular septal ruptures are caused by the same factors that lead to other ventricular ruptures. These patients live longer after rupture, and the diagnosis can be made clinically without great difficulty.

7. Extra precautionary clinical care, to prevent rupture, should be given patients whose blood pressure remains elevated after coronary thrombosis.

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THE EFFECTS OF REPEATED ADMINISTRATION OF LANATOSIDE C ON THE MYOCARDIUM OF THE DOG

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INTRODUCTION

THE ability of digitalis substances to produce changes in the myocardium of the experimental animal has been studied by several investigators.[1] After the administration of sublethal or lethal doses of preparations of digitalis purpurea, digitoxin, and strophanthin to various species, but chiefly to cats and dogs, microscopic examination of the heart muscle has disclosed areas of focal necrosis, cellular infiltration, interstitial edema and fibrosis, and hyaline degeneration. These changes have been found most commonly in subendocardial areas, especially in the ventricular musculature.

The effect on the dog's myocardium of lanatoside C, a crystalline derivative of digitalis lanata, has been studied by Fahr and LaDue,[2] and by LaDue.[3] The first[2] of these reports dealt with several dogs, but apparently in only one of them was intravenous administration employed. Examination of the myocardium yielded negative results. LaDue studied the effects of toxic and lethal intravenous doses of lanatoside C in a series of nine dogs. In each animal, marked constitutional effects were produced, including anorexia, emesis, and weight loss. With the exception of two dogs, no experiment was carried beyond eight days. In each case, myocardial damage was found by microscopic examination, and "electrocardiographic changes" were "present."[3] In a more recent report, LaDue confirmed these conclusions and reported that the simultaneous subcutaneous administration of atropine to dogs which were receiving daily intravenous injections of lanatoside C resulted in a markedly increased survival time for the animals.[12]

PROBLEM AND METHOD

Recent appraisals of the clinical usefulness of lanatoside C, especially its relatively low toxicity[2] and the rapid dissipation of its lethal effect on animals,[4] prompted us to study the effects of long-continued administration of this substance on the dog's heart, excluding as far as possible the factors of vomiting, malnutrition, and depletion. The dog has been shown to be a reliable animal for the assay of digitalis substances, and exhibits a smaller standard deviation to toxic and lethal dosage than does the cat.[4]

Kaplan and Visscher[6] ascertained that the M. L. D. of lanatoside C by intravenous injection is 0.36 mg. per kg. when no anesthetic is used. They found that the majority of dogs vomited when between 20 per cent and 30 per cent of the M. L. D. was injected, and that, in all cases, vomiting occurred when 30 per cent to 36 per cent of the M. L. D. was given.

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Thirty per cent of the M. L. D., accordingly, was selected for both lanatoside C. and digitoxin as the dose for study in these experiments, with the hope that it would be possible to maintain at least some of the animals over a substantial period of time while toxic doses were being given.

Normal adult male dogs were used. The animals were weighed and were injected intravenously three times a week. The dosage, of course, was determined by the current weight. Vomiting and salivation were constant reactions to each injection, and followed the injection within a few minutes. Injections were given in the mornings and feedings in the late afternoon, by which time appetite had often been regained. Muscular weakness, diarrhea, tachycardia, and ectopic beats were observed in some of the animals. Other animals appeared to remain unaffected, except for the salivation and vomiting immediately after the injection. Several experiments were terminated by the spontaneous death of the animals, and others by sacrificing the animals (by bleeding) after varying periods of administration. The diet consisted of a "complete" proprietary food mixture.

Electrocardiographic changes as a result of giving lanatoside C have been found in dogs by LaDue.[3] Others[2, 7] have described digitalis-like effects of this drug on the electrocardiogram in the human being. Electrocardiograms were made on some of our animals before and during the administration of the drugs, but changes caused by positional influences dominated the records to such an extent that they were not considered suitable for the interpretation of digitalis effects.

Lanatoside C, in common with other digitalis preparations, has characteristics of potency which must be expressed differently for different methods of assay,[8] and in our experiments, therefore, dosage is expressed only in terms of weight.

Methodical sectioning of the myocardium, according to the method of Hu, et al.,[1-d] was employed.

LANATOSIDE C

Eight dogs were given 0.3 M.L.D. of lanatoside C; that is, 0.108 mg. per kg., by intravenous injection, for periods ranging from twenty-one to ninety-four days.

Of the eight dogs, two (4, 47) showed appreciable changes in one section only. Three dogs (95, 99, 25) showed slight abnormalities in one or two sections, and two were negative throughout (96, 98), as shown in Table I. Four of the eight animals were sacrificed at intervals varying from thirty-eight to ninety-four days. The remaining four, which were found dead, had received lanatoside C for twenty-one to eighty-four days. No animal was included in which post-mortem changes made microscopic examination difficult.

Fig. 1 shows a typical area of necrotic muscle (Section 4-2), rather sharply outlined with fine proliferation of fibroblasts and small capillaries (early granulation tissue). There are remnants of muscle fibers, and the cellular arrangement is mainly mononuclear. This section was taken from the posterior portion of the left ventricular wall of a dog which had received twelve injections of lanatoside C over a period of four weeks.

Fig. 2 shows a section of normal myocardium which was typical of the lack of abnormality in all sections from a dog (38) which had received forty injections over a period of ninety-four days.

Table I shows the weight changes. Extreme loss of weight occurred in only one dog; it suffered from distemper as a terminal illness (96),

TABLE I

DRUG USED AND DOSE	DOG NO.	WEIGHT AT BEGINNING OF EXPERIMENT, (AND NET CHANGE) KG.	REGIONS OF MICROSCOPIC STUDY* (SECTIONS)							NO. OF INJECTIONS	DURATION OF EXPERIMENT
			L.V.A.	L.V.P.	L.V.L.	V.S.	R.V.	R.A.	L.A.		
	95	9.0 (–0.9)	0	0	0	+	0	0	0	15	5½ wks. (sacrificed)
Lanatoside C	96	9.5 (–5.4)	0	0	0	0	0	0	0	7	7 wks. (died; distemper, terminally)
0.108 mg/kg.	99	10.1 (–0.1)	0	0	0	+	0	+	0	31	84 days (sacrificed)
(0.3 M. L. D.)	4	17.3 (–2.7)	0	++	0	+	0	+	0	12	4 wks. (found dead)
	25	11.4 (–2.3)	0	0	+	0	0	0	0	9	21 days (found dead)
	38	13.2 (–0.9)	0	0	0	0	0	0	0	40	94 days (sacrificed)
	46	11.4 (+0.9)	0	++	0	0	0	0	0	40	92 days (sacrificed)
	47	13.6 (–1.8)	0	++	0	0	+	0	0	8	18 days (found dead)
Digitoxin	97	21.8 (–0.4)	+	+	++	0	0	0	0	7	4 wks. (found dead)
0.15 mg/kg.	100	11.8 (–1.8)	0	0	++	0	0	+	+	12	6 wks. (sacrificed)**
(0.3 M. L. D.)											

0 = normal myocardium; + and + + = slight and moderate myocardial changes, as described in text.
*L.V.A. = Anterior portion left ventricle; including anterior papillary muscle.
L.V.P. = Posterior portion left ventricle; including posterior papillary muscle.
L.V.L. = Lateral left ventricular wall.
V.S. = Anterior portion of interventricular septum.
R.V. = Anterior right ventricular wall.
R.A. = Right auricular wall, including appendage.
L.A. = Left auricular wall, including appendage.
**Animals were sacrificed by bleeding.

and showed no myocardial abnormality. In the remaining animals, the change of weight varied from a moderate loss to a slight gain.

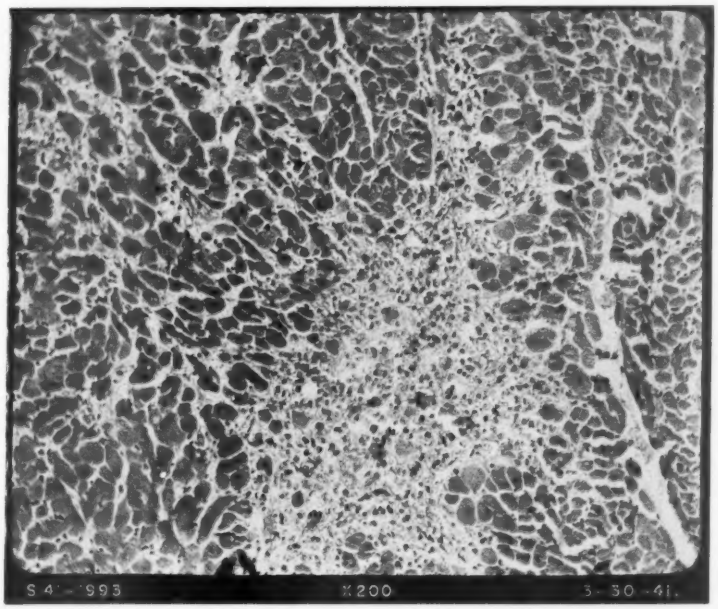

Fig. 1.—Dog No. 4, Section 2. From posterior portion of the left ventricle, showing focal necrosis, mononuclear infiltration, and early granulation tissue; from a dog which had received twelve injections (0.3 M. L. D. each) of lanatoside C in a period of four weeks.

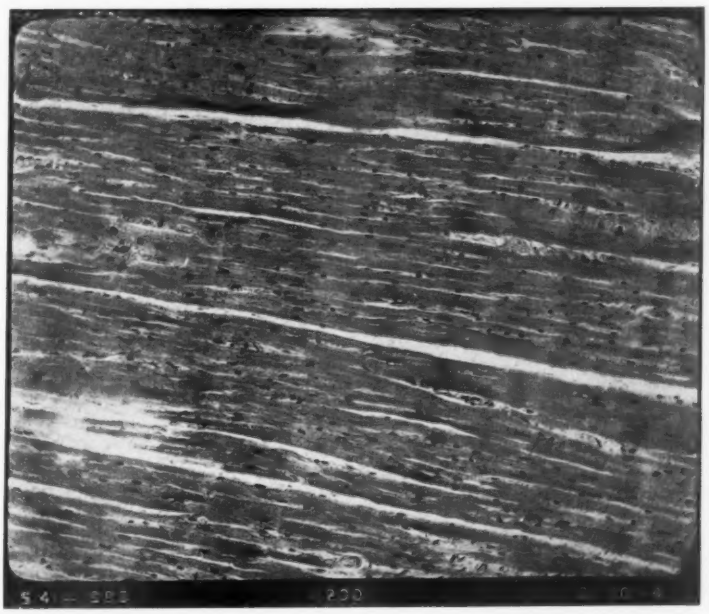

Fig. 2.—Dog No. 38, Section 2. From posterior portion of the left ventricle, showing normal myocardium; from a dog which had received forty injections (0.3 M. L. D. each) of lanatoside C in a period of ninety-four days.

DIGITOXIN

The M. L. D. of digitoxin for dogs has been ascertained[9] and the effect of its injection on the heart muscle has been fairly well standardized.[1] We attempted to compare its effect with that of lanatoside C by using comparable doses of digitoxin, i.e., 0.3 M. L. D. in a parallel series. The relative unavailability of this substance at the present time, however, permitted its use in only two dogs. A review of the work of Hu, et al.,[1-d] discloses the usual pathologic changes which follow the administration of digitoxin to dogs when a technique rather similar to ours is employed.

Of our two animals which received digitoxin, one died after seven injections, and the other was sacrificed after twelve injections. In each case, the dose was 0.150 mg. per kg. of body weight. Table I shows the histopathologic changes in the myocardium of each. These changes consisted of subendocardial necrosis, with mononuclear and polymorphonuclear infiltration, as described by Hu, et al.[1-d]

Table I shows that there was no marked loss of weight in either animal.

DISCUSSION

Table I shows that, in general, when the total nutrition of the animals was maintained in good or fair condition, the pathologic changes in the myocardium were not extensive, especially in the animals to which lanatoside C had been administered. This was true even in dogs which had received toxic doses of the drug over periods as long as ninety-four days. In fact, the dog which was maintained for the longest time showed no abnormalities in the heart muscle. The rapid dissipation of the lethal effect of large doses of lanatoside C in cats in comparison with other digitalis glycosides has been measured by DeGraff and Lehman.[4]

No relationship could be established between the histologic changes in the myocardium and the spontaneous death of an animal. Extracardial lesions (cerebral, suprarenal, hepatic, and renal), as described by Hueper and Ichniowski,[10] may play an important part in causing death after digitoxin administration. These authors believed that some of these dogs showed no myocardial change. Also, no relationship could be found between the number of injections and the pathologic changes. As noted by Hu, et al.,[1-d] the lesions tend to occur in the ventricles, especially the left. In our animals, no special disease of the coronary arteries or of the Purkinje tissues was found. The changes which have been described have not been seen in the hearts of normal dogs.[1-d] The mechanism of the production of these lesions is not clearly understood. They may be the direct result of toxic action of the drug on the muscle fibers, or of foci of myocardial ischemia as a result of insufficiency of coronary flow caused by increased myocardial tone. However, moderate doses of lanatoside C or other digitalis bodies do not restrict coronary flow, as measured by the thermostromuhr, in dogs.[11]

CONCLUSIONS

1. Repeated toxic doses of lanatoside C and of digitoxin were given intravenously to dogs. The attempt was made (by spacing the injections and by the use of an adequate diet) to interfere as little as possible with the nutrition of the animals.

2. Focal myocardial necrosis was found in each of two dogs which had received digitoxin, and to a relatively lesser extent in six of eight dogs which had been given lanatoside C; the two remaining dogs showed no change in the myocardium.

3. No relationship could be established between the clinical condition of the animals and the myocardial changes.

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SYPHILITIC CORONARY STENOSIS, WITH MYOCARDIAL INFARCTION

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IT IS generally conceded that syphilis of the cardiovascular system affects the heart and contiguous structures in at least six ways. There may be (a) aortitis, with inflammation of the adventitia, media, and intima; (b) aortic aneurysm, either diffuse or saccular; (c) valvulitis or inflammation of the aortic ring, producing regurgitation; (d) coronary arteritis, producing stenosis of the ostia of the arteries; (e) myocarditis, producing either diffuse or gummatous lesions; and (f) syphilitic coronary arteritis, resulting in myocardial infarction. It is our purpose to discuss the latter condition as found at Charity Hospital among 6,225 routine, consecutive autopsies, performed between January 1, 1937, and January 1, 1942; and to record a specific instance of this condition.

STATISTICS

During the past five years, 287,257 patients, about half of whom were colored, entered the wards of Charity Hospital; 21,642 (7.5 per cent) of these were discharged with a clinical diagnosis of heart disease. Of this group with heart disease, 326 (1.5 per cent) had myocardial infarction resulting from a variety of causes, and of these only 3 (0.9 per cent) had myocardial infarction secondary to syphilitic coronary stenosis. Among the 6,225 consecutive routine autopsies, there were 4,610 (74 per cent) with a post-mortem diagnosis of heart disease, in 185 (4.0 per cent) of which myocardial disease of various kinds caused death; in only three (1.6 per cent) of these was infarction produced by syphilitic coronary narrowing; therefore, myocardial infarction as a result of syphilis is rare.

Of the total number of autopsies, in 193 (3.1 per cent) there was syphilitic aortitis. Forty (20.7 per cent) of the patients with aortitis had narrowing of one or both coronary arteries as a result of syphilitic infection of the aorta, and only 3 (7.5 per cent) of these had myocardial infarction secondary to the stenosis. Of the 193 patients with syphilitic aortitis, only 3 (1.5 per cent) died of myocardial disease caused by coronary narrowing. The incidence of aortitis in routine autopsies, as reported by other observers, varies from 2.7 per cent to 7.0 per cent,[1, 2] whereas that of aortitis with syphilitic coronary narrowing varies between 8.4 per cent and 35.0 per cent.[3, 4] Figures from selected sources are shown in Table I.

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TABLE I

THE INCIDENCE OF (1) SYPHILITIC AORTITIS AND (2) SYPHILITIC AORTITIS WITH SOME DEGREE OF STENOSIS OF THE CORONARY ORIFICES, FROM VARIOUS REPORTS OF AUTOPSIES

SYPHILITIC AORTITIS		SYPHILITIC AORTITIS WITH CORONARY STENOSIS	
AUTHOR	PER CENT	AUTHOR	PER CENT
Cormia[1]	2.7	Carr[3]	8.4
Burch and Winsor	3.1	Reid[5]	12.8
Reid[5]	3.2	Martland[9]	14.9
Symmers[6]	3.5	Clawson and Bell[10]	19.9
Cowan and Faulds[7]	6.0	Burch and Winsor	20.7
Pincoffs and Love[8]	6.9	Saphir[11]	31.0
Oberndorfer[2]	7.0	Bruenn[12]	33.1
		Saphir and Scott[4]	35.0

The relative importance of myocardial infarction in patients with syphilis of the cardiovascular system is shown by the fact that about one-fifth of the patients with syphilitic aortitis have involvement of the coronary ostia, whereas only one or two per cent with syphilitic aortitis have myocardial infarction. Seven or eight per cent of the group with coronary narrowing, however, have myocardial infarction. Only six cases of cardiac infarction from syphilitic coronary stenosis were found in the literature during the past ten years. Bruenn[12] studied 39 autopsies on patients with coronary stenosis and found that three of these had myocardial infarction. Saphir[11] described one such case. Briskman[13] described two patients who probably had myocardial infarction. Norris[14] described three patients with myocardial change, but doubted that coronary occlusion was the etiologic factor.

The average age of the patients in the Charity Hospital series who had syphilitic coronary narrowing was 45 years. The youngest person with this condition was 20, and the oldest, 70. Seventy-five per cent of the 40 patients were between the ages of 30 and 60. This fits in well with the expected time of appearance of cardiovascular syphilis.

Both of the coronary ostia were involved in 29 (72.5 per cent) of the patients who had some degree of stenosis of the coronary orifices. The right alone was involved in 7 (17.5 per cent) and the left in 2 (5.0 per cent). Love and Warner[15] reported 15 autopsy cases of syphilitic coronary stenosis. In 8 (53.3 per cent) of these there was stenosis of both coronary ostia, in 6 (40.0 per cent), stenosis of the right coronary orifice only, and in one (6.6 per cent), narrowing of the left coronary orifice.

The race distribution of the 40 patients with coronary stenosis at Charity Hospital was 6 white and 34 colored, a ratio of about 1 to 6. Of the three with myocardial infarction, all were colored. The sex distribution of the patients was 9 females and 31 males, a ratio of about 1 to 3.5.

The Wassermann reaction was recorded in 27 of the 40 patients with syphilitic coronary stenosis; it was positive in 26 (96.3 per cent). Pincoffs and Love[8] state that a positive blood Wassermann reaction is a valuable diagnostic sign; the reaction was positive in all of their autopsied patients who had narrowing of the coronary arteries caused by syphilis.

The weight of the heart varied, depending on whether or not there was: (a) aortic regurgitation, (b) hypertension, (c) aortic regurgitation and hypertension combined; (d) syphilitic coronary stenosis, or (e) aortic aneurysm. These variations are shown in Table II.

TABLE II

HEART WEIGHTS (GRAMS) IN FORTY CASES OF SYPHILITIC CORONARY STENOSIS, CORRELATED WITH CERTAIN ASSOCIATED ABNORMAL STATES

PATHOLOGIC STATE	NO. OF CASES	MEAN HT. WT.	MINIMUM HT. WT.	MAXIMUM HT. WT.
1. Aortic regurgitation and essential hypertension	2	798	650	945
2. Essential hypertension	5	634	330	900
3. Aortic regurgitation	20	609	315	945
4. Syphilitic coronary stenosis alone	4	413	220	500
5. Aortic aneurysm	2	288	220	355

Although the number of cases is small, the data tend to indicate that the heaviest hearts were from patients who had a combination of aortic regurgitation and essential hypertension. Either of these conditions alone generally resulted in a marked increase in cardiac weight. The average weight when coronary stenosis was associated with hypertension, aortic regurgitation, or a combination of these conditions, was 680 grams. In two cases, aortic aneurysm did not produce an increase in cardiac weight (average for the two hearts, 288 grams). Coronary stenosis alone, however, was associated with an average heart weight midway between these two figures, namely, 413 grams. These figures agree with those of Bruenn.[12] He found that the heart with syphilitic coronary stenosis was only moderately enlarged (largest, 420 grams) whereas the heart with coronary stenosis associated with aortic regurgitation was greatly enlarged.

The following case illustrates the clinical picture of myocardial infarction caused by syphilitic obstruction of the coronary orifices.

REPORT OF CASE

L. A., a 39-year-old colored woman, married, a shrimp worker, entered the Charity Hospital November 7, 1941, and died November 8, 1941.

The patient had been well until six weeks before entrance, when she first noted pain in the chest and dyspnea which came on suddenly after meals or exertion. The pain was most intense about the lower end of the sternum, and radiated to the left shoulder and down the arm to the level of the elbow. The pain was sudden in onset, vise-like in character, and severe enough to produce crying. It frequently

lasted fifteen to twenty minutes. She had two or three such attacks daily, and they increased in frequency and duration until the day of the admission, at which time she experienced the most excruciating attack she had ever had. At this time she coughed up some blood-tinged sputum.

There was no history of syphilis. On October 12, 1941, her blood Wassermann reaction was positive. An electrocardiogram on the same date showed only left axis deviation.

On entrance her temperature was 99.2° F., her pulse rate, 120 per minute, her respiratory rate, 30 per minute, and her blood pressure, 115/80. She was moderately obese, and was sitting in bed gasping for breath. The pupils were circular, equal, and reacted well to light and accommodation. The heart was moderately enlarged to the left. A soft systolic murmur was heard at the mitral area. The pulmonic second sound was louder than the aortic second sound. Fine moist râles were heard throughout both lungs posteriorly. The liver was palpable four centimeters below the costal margin. Slight edema of the ankles was present.

The patient was treated with digitalis, aminophyllin, oxygen, and hypertonic glucose solution intravenously. She became increasingly dyspneic and edematous, and coughed up some bloody, frothy material. She died suddenly November 8, 1941, after six hours of hospitalization.

Necropsy.—The heart weighed 350 grams. It was dilated and flabby. There was definite evidence of infarction of the major portion of the left ventricle and the lower portion of the interventricular septum. The aortic valves were slightly thickened and the commissures were negligibly widened. Both coronary ostia were markedly narrowed at the aortic wall, but beyond this point the vessels were widely patent. No emboli were found. The circumference of the aortic ring was not enlarged. The aorta showed typical oak-bark wrinkling at the root. Circumscribed, elevated, edematous plaques were seen in the first part of the aorta and in the sinuses of Valsalva.

Microscopically, the cardiac muscle was edematous, and many of the fibers showed hyalinization and necrosis. The endocardium was thickened by the presence of fibrin, round cells, and some polymorphonuclear cells. The aorta was the seat of intimal thickening and infiltration with lymphocytic cells. The vasa vasorum showed intimal thickening and perivascular collars. Lymphocytic infiltration was most marked in the tissue between the adventitia and media.

DISCUSSION

The history of severe precordial pain, referred to the inner aspect of the left arm, in a middle-aged colored person with a positive Wassermann reaction and no arteriosclerosis or hypertension suggests the possibility of syphilitic coronary narrowing. This patient presented such a picture. Bruenn[12] states that precordial pain is the presenting complaint of the majority of patients with the syphilitic coronary syndrome; twenty-three of his thirty-five patients with coronary stenosis had anginal pain. It must be borne in mind, however, that many patients with coronary stenosis, and even those with complete closure of both coronary ostia (vide infra), may have no precordial pain of any kind. On the other hand, syphilitic aortitis, with or without aneurysm or aortic insufficiency, and numerous nonsyphilitic states may produce precordial pain which is indistinguishable from that characteristically produced by syphilitic coronary stenosis. The race and age of the patient[16] suggested the possibility of syphilis as a cause of coronary

stenosis. The positive Wassermann reaction was highly compatible with syphilitic coronary stenosis, as pointed out by Pincoffs and Love[8] and as shown by the records from Charity Hospital. The size of the heart was in keeping with syphilitic coronary stenosis. The short course of her illness (only six weeks from the onset of the precordial pain), the typical pain of coronary occlusion, the lack of response to treatment, the history of infrequent previous hospital admissions, and the fact that the patient grew worse rapidly fitted in well with the diagnosis of syphilitic coronary stenosis with myocardial infarction.

PATHOLOGY

A vascular phenomenon underlies many of the pathologic changes in both the early and late stages of syphilitic disease. Any organ of the body may be involved, and numerous dissimilar lesions are frequently produced. Coronary occlusion, aortic aneurysm, cerebral hemorrhage, primary chancre, gastric ulcer, and necrosis of gummata are secondary to vascular changes, and all present the picture of a productive obliterating arteritis which involves all three coats of the arteries.[17, 18] Such lesions may obstruct the coronary, carotid, innominate, or spinal arterial ostia, or they may weaken their walls to produce aneurysm or dilatation.[19]

Microscopically, the adventitia of the coronaries shows an accumulation of small round cells, particularly about the vasa vasorum. Moritz[20] states that the inflammation usually begins about the vasa vasorum in the adventitia of the vessel. This process penetrates the media and intima by extension of the inflammation along the smaller vessels.[19] The media becomes infiltrated with lymphocytic and small round cells which replace the healthy muscle and elastic tissue. The intima is greatly thickened as a result of the formation of succulent vascular inflammatory plaques which occlude the ostia of the coronary arteries at the point where they pass through the aortic wall. Such exudative, edematous lesions may encircle the aortic root, forming the so-called "girdle of Venus."[18] When the coronary ostia are involved, usually only the first 30 millimeters of the artery are affected, and beyond this point the vessel widens and remains patent throughout its entire length. Involvement of the distal branches is rare.[9, 10, 20-26] Cormia,[1] however, states that the distal portions of the coronary arteries are involved in 23 per cent of the cases of narrowing of the coronary ostia caused by syphilitic aortitis.

The high incidence of coronary stenosis is due, in large part, to the location of the coronary ostia in the aortic wall, as well as to the distribution of the blood supply of the coronary ostia and aortic root. The locations of the coronary orifices are not constant. Ordinarily, they are within the sinuses of Valsalva, but this is by no means invariable. Occasionally they are found one or two centimeters above the sinuses, in which case they are more easily involved in the syphilitic

infiltration at the root of the aorta.[27] Wearn[28] states that the high incidence of ostial involvement is due to the fact that a branch of the coronary artery supplies the first part of the aorta in the region where aortitis is most common.

The time of appearance of syphilitic coronary stenosis in cases of syphilitic aortitis is often early in the course of the disease, for stenosis is sometimes found in an aorta which is almost free from syphilitic involvement.[20]

It is frequently difficult to distinguish between syphilitic and arteriosclerotic coronary disease, for, in either case, plaques are formed which may be similar in appearance and location. Fatty changes and calcification may occur in either condition. In syphilis the inflammatory process extends from the adventitia to the intima, and a fibrotic exudative change takes place within all the vascular coats. Fatty change, with cholesterolization and calcification of all arterial structures, may result secondarily. In arteriosclerosis the fatty change takes place early in the intima, and a superficial fibroblastic change, which penetrates no deeper than the intima, occurs later. Frequently, both a syphilitic and arteriosclerotic process are present.[13] Leary[18] states that arteriosclerotic changes are frequently engrafted upon old syphilitic lesions, and, as these regress, the arteriosclerotic changes become more prominent. There are, however, certain abnormalities in the cardiovascular system which help to distinguish between syphilitic and arteriosclerotic coronary disease. In syphilis, the coronary arteries show thickening of all three coats, longitudinal wrinkling of the intima, edematous plaques about the ostia of the arteries, and patency of the terminal portion of the artery. There are perivascular round cell infiltration and, more rarely, gummata about the coronary ostia. In arteriosclerosis there are no Longcope plaques, nor is there wrinkling of the intima. The coronaries are tortuous, hard, and brittle, and contain firm yellow plaques which extend throughout the length of the artery.[22] Glistening fibrous tissue is sometimes found in the left ventricular musculature.

The myocardial change which results from coronary arteriosclerosis and syphilitic coronary stenosis may be similar. Fibrosis and lymphocytic infiltration of the myocardium will be found if cardiac ischemia has been present. If a sudden coronary stenosis had taken place, myocardial infarction would be present provided death had not occurred too suddenly. In patients with syphilitic coronary stenosis there is no essential relationship between coronary closure and myocardial change. This is because of the insidious involvement of the arteries and the rich collateral circulation which develops. Briskman[13] described four patients with syphilitic coronary stenosis who died suddenly. At necropsy two showed atrophy of the myocardium and one myocardial fibrosis, and, in one, the myocardium was unaltered.

The collateral circulation which results from slow coronary occlusion is extensive.[29, 30] Wearn, et al.,[31] have shown by injection methods that

the artero-luminal, artero-sinusoidal and Thebesian vessels, all of which run between the coronary vessels and chambers of the heart, are probably active in such cases. Pratt[32] was able to keep a cat heart beating for one hour by perfusing blood through the auricles and ventricles. This seems to indicate that the cardiac musculature can be nourished by blood passing through the chambers of the heart, and is not entirely dependent upon blood entering through the coronary vessels. In syphilitic coronary stenosis the vessel is usually patent beyond the obstruction at its orifice. This suggests that blood flows through these vessels, although the coronary ostia may be completely closed. Leary[18] states that collateral vessels develop through the pericardial, bronchial, and aortic vasa vasorum, and contribute to the nutrition of the heart when coronary stenosis exists.

DIAGNOSIS

Syphilitic coronary stenosis with or without varying degrees of myocardial infarction is frequently suspected clinically, but the diagnosis may be impossible to prove. In general, anginal pain, a moderately enlarged heart, and a positive Wassermann reaction in a young male Negro, who responds poorly to digitalis or antisyphilitic drugs and grows worse rapidly, should indicate the presence of syphilitic coronary stenosis. If, in addition, there are shock, hypotension, muffled heart tones, a pericardial friction rub, leucocytosis, and an elevated sedimentation rate, myocardial infarction secondary to syphilitic coronary narrowing should be considered. In such cases, however, death may occur so rapidly that these typical signs of myocardial infarction do not have time to develop.

Syphilitic coronary stenosis is found in relatively young persons. Bruenn[12] states that the average age is 34 years. At Charity Hospital the age of the patients varied between 30 and 60. The patients with syphilitic aortitis reported by Longcope[19] were in a similar age group, i.e., between 30 and 50. Patients with arteriosclerotic coronary disease are likely to be older.

Syphilitic coronary stenosis is frequently associated with aortic regurgitation. This is important because patients with the latter condition should be suspected of having involvement of their coronary arteries. Eighty-seven and one-tenth per cent of Bruenn's[12] patients with syphilitic coronary stenosis also had involvement of the aortic valves, and 76 per cent of the patients at Charity Hospital with coronary stenosis had definite aortic regurgitation. When aortic insufficiency is found in a young, white person it is likely to be the result of rheumatic fever, which only rarely involves the coronary arteries, whereas aortic regurgitation in a young, colored person is more likely to be syphilitic. At Charity Hospital, the coronary arteries showed syphilitic involvement six times more frequently in the colored race than in the white.

The pain caused by syphilitic coronary stenosis frequently simulates angina pectoris. It develops suddenly, is viselike in character, and tends to radiate from the precordium to the arm, neck, back, or epigastrium. It generally lasts from a few seconds to a few minutes and is precipitated by eating or exercise. Pinceffs and Love[8] found that 86.6 per cent of their patients with syphilitic coronary stenosis had typical angina. They state that anginal pain is rare in patients with uncomplicated aortitis, but is common in those with syphilitic coronary stenosis. Anginal pain may, however, be present with other forms of cardiovascular disease. If angina occurs in a patient under 40 years of age with a positive Wassermann reaction, the pain is probably syphilitic in origin; if the patient is over 40, it is probably caused by coronary arteriosclerosis.[8] Willius[33] states that angina of over ten minutes' duration is likely to be caused by organic coronary change, and is indicative of syphilitic stenosis if the patient is a young Negro. Longcope[19] states that the pain of aortitis is produced by inflammation at the root of the aorta or by bronchospasm. This type of pain may be confused with the anginal pain caused by coronary involvement. Typically, the pain associated with aortic regurgitation or aortic aneurysm does not tend to radiate. It is present as a constant, viselike, substernal oppression. On the other hand, there may be extensive involvement of the root of the aorta or complete stenosis of both coronary ostia without any pain whatsoever.[34] Albutt[34] states that a man may be fairly comfortable with both coronary ostia completely occluded. Kokita[27] reported a patient with acute congestive heart failure without angina pectoris who had complete occlusion of one coronary orifice.

The mechanism of the production of the pain is not clear. Leary[35] states that coronary spasm is a factor in producing angina and sudden death. Lewis[36] and Katz[37] state that myocardial ischemia produces circulatory metabolites which are responsible for the pain. Norris[38] believes that the pain is caused by inflammation of the pericoronary nerves. These factors are probably important, but they do not explain all clinical or experimental observations.

Cardiac enlargement, we found, is only moderate in cases of uncomplicated syphilitic coronary narrowing. This is in agreement with Bruenn,[12] who states that the largest of thirty-nine hearts which were the seat of coronary stenosis weighed 420 grams; the average was 370. In the Charity Hospital study the greatest heart weight with uncomplicated coronary narrowing was 500 grams, and the average was 413 grams. The cause of this moderate hypertrophy is not clear. It has been suggested that myocardial ischemia tends to prevent cardiac hypertrophy. This explanation is inadequate.

Patients with coronary stenosis and aortic regurgitation, coronary stenosis and essential hypertension, or coronary stenosis, aortic regurgitation, and essential hypertension had very heavy hearts; the average was 680 grams, and the greatest, 945 grams. The largest hearts are

generally produced by rheumatic heart disease, arteriosclerosis, hypertension, and aortic regurgitation. These may weigh nearly 1,000 grams.[38] Such cardiac enlargement is not usually caused by uncomplicated coronary stenosis. On the other hand, if coronary stenosis is associated with aortic aneurysm, the weight is not increased markedly. In this group the average weight was 288 grams, and the greatest weight was 355 grams.

The blood Wassermann reaction, if it is positive, is a valuable suggestive sign of cardiovascular syphilis, and more particularly of coronary stenosis. Scott[39] states that 10 per cent of patients with aortitis have a negative Wassermann reaction. Longcope[19] found positive Wassermann reactions in 75 per cent of his patients with cardiovascular syphilis, and Warr[16] found positive reactions in 74 per cent. Pincoffs and Love[8] state that the complement fixation test was positive in all of their patients with syphilitic coronary stenosis. At Charity Hospital, 96.3 per cent of twenty-six patients with coronary stenosis had a positive Wassermann reaction in spite of the fact that most of these patients had had some antisyphilitic treatment.

The electrocardiogram usually gives little evidence of syphilitic coronary involvement. Although little is known concerning the electrocardiographic changes secondary to syphilitic coronary narrowing, one would expect them to be similar to those which occur with myocardial ischemia or myocardial infarction resulting from other causes. Bruenn[12] reported left axis deviation and abnormal T waves in a significant number of patients with coronary stenosis and aortic regurgitation. Juster and Pardee[40] reported abnormal T waves in 85 per cent of thirty-five patients with syphilitic aortitis. Willius[33] states that a negative T_1 and T_2 are common in cases of obliterative arterial disease of the left coronary artery, and that this indicates myofibrosis or a healed or healing myocardial infarct. Moritz[20] reported three patients with coronary arteritis who died suddenly; all had normal electrocardiograms and two had angina, but at necropsy neither showed any evidence of myocardial infarction. The three patients with myocardial infarction at Charity Hospital died so quickly that electrocardiograms could not be taken.

It is often difficult to differentiate syphilitic coronary stenosis from conditions which resemble it. (1) In simple aortitis, precordial pain is usually absent, the T waves in the electrocardiogram are not abnormal, and the aortic second sound is usually not tympanitic. (2) In aortic aneurysm, a fusiform or saccular dilatation of the aorta may be seen roentgenographically or fluoroscopically, and the aortic second sound usually is tympanitic. Diadrast may be used to outline the aortic enlargement, and pain, if present, is usually constant and nonradiating. Pressure phenomena may complicate the picture. (3) In aortic insufficiency, a large, forcefully beating heart and prominent peripheral signs are observable. The pain is usually constant, but may be anginal in character. The response to treatment is poor, and the patient is

usually admitted to the hospital only once. The life expectancy is somewhat more than a year from the onset of symptoms. Sudden death may ensue. These patients have a high incidence of concomitant coronary stenosis. (4) Pure coronary stenosis shows itself clinically as angina, dyspnea on exertion, or paroxysmal nocturnal dyspnea. The response to treatment is poor, and the life expectancy is approximately three months after the onset of symptoms. The patient is usually under 40 years of age, and a positive Wassermann reaction is common. A relatively slow death, with congestive heart failure, is the rule; however, sudden death from anginal failure may occur. The heart is usually only moderately enlarged. When the myocardium becomes rapidly involved as a result of coronary stenosis, there may be a history of sudden, agonizing, precordial pain which lasts for more than ten minutes. Fever, leucocytosis, an elevated sedimentation rate, electrocardiographic changes, a friction rub, and an enlarging heart indicate the presence of myocardial infarction. Other signs of myocardial infarction are a low systolic blood pressure, a diffuse apical thrust, muffled heart tones, dyspnea, edema, orthopnea, pulmonary hypertension, paroxysmal nocturnal dyspnea, gallop rhythm, and heart block or Stokes-Adams attacks. Auricular fibrillation is unusual.

PROGNOSIS

Patients with cardiovascular syphilis die more frequently from their cardiac disease than from intercurrent illnesses. Cormia[1] states that, of 199 patients with cardiovascular syphilis, all but six died of heart disease. Sudden death has been defined as that which occurs within six hours from the onset of symptoms. In cardiovascular syphilis, death is usually sudden and may be caused by a variety of conditions: (1) A ruptured aortic aneurysm may discharge its contents externally, into the pleural space, trachea, bronchi, esophagus, mediastinum, or the pulmonary artery. Death is usually sudden except in the latter case, in which the patient may live for months. (2) A dissecting aneurysm, beginning with rupture of an aortic vasa vasorum and dissection of blood into the pericardial space, may produce cardiac tamponade. Death is usually sudden, but it may be slow if the hemopericardium develops slowly and the pericardial membrane stretches greatly. (3) Congestive heart failure caused by aortic regurgitation or ruptured aortic valve cusps may occur. Death is sometimes sudden, but it is more usually slow and is caused by the low diastolic blood pressure, with poor coronary circulation. (4) Congestive heart failure secondary to myocardial syphilis usually causes death within two or three months. (5) Coronary embolism resulting from thrombosis in the area of aortitis causes sudden death.[41] (6) A Herxheimer reaction produces death in a few hours. (7) Lastly, coronary stenosis with or without myocardial infarction may be a cause of death. In the latter group, sudden death may occur, but a rapidly fatal course is more common. Pincoffs and Love[8] reported

six patients with coronary stenosis who lived an average of 2.3 months after the onset of symptoms. They grew worse rapidly and did not respond to treatment. Bruenn[12] states that the average length of life after cardiac symptoms appear in patients with coronary stenosis is 3.2 months. Patients with coronary stenosis and myocardial infarction are likely to die suddenly. Of the three patients with myocardial infarction caused by syphilitic coronary stenosis in the Charity Hospital series, one was sitting in bed when he developed acute congestive heart failure; he died about six hours later. One patient was kneeling in church when she was struck with precordial pain. She died within the hour in the emergency room at Charity Hospital. The third patient had acute congestive failure when he entered the emergency room and died before he could be admitted to the ward. All three of these hearts showed gross and microscopic evidence of infarction.

SUMMARY

The protocols of 6,225 consecutive autopsies at the Charity Hospital of New Orleans during the past five years were reviewed in order to ascertain the incidence of myocardial infarction secondary to syphilitic coronary stenosis. Three such patients were found. These comprised 1.6 per cent of all cases of myocardial infarction. A review of the literature revealed nine other patients with myocardial infarction caused by syphilis.

The average age of the patients with syphilitic coronary stenosis was forty-five years. Both arteries were involved in the majority of cases. Among the patients with coronary stenosis, the white to colored ratio was about one to six, and the female to male ratio was about one to three and a half. The blood Wassermann reaction was positive in 96.3 per cent of the patients with coronary stenosis. The average weight of the hearts with coronary stenosis alone was 413 grams, whereas patients who had had coronary stenosis and aortic regurgitation, hypertension, or both, had an average heart weight of 680 grams.

A case of myocardial infarction secondary to syphilitic coronary stenosis was described to illustrate the clinical picture.

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CONGENITAL AORTIC AND MITRAL ATRESIA

Report of a Case and Review of the Literature

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REVIEW of the literature shows that complete mitral and aortic atresia is a relatively rare condition. A case in which there were these and associated anomalies led us to study the variants described by others, and to summarize their work in relation to our observations.

CASE REPORT*

The patient, a white female child, five days old, was born spontaneously and was apparently normal, evidencing the usual color, cry, and activity. On the day after birth, it was noted that the child was pale but nursed well. On the second day after birth, the infant had to be urged to nurse. On the third day, there was evidence that it tired very easily while feeding and that its color remained very pale. The child was listless for the greater part of the third day, and, in the evening, when the temperature fell to 97° F., warm blankets were applied. On the fourth day, it was noted that respiration was rapid, shallow, and labored. In addition, cyanosis was present, and the baby continued to be cold. Breast milk was refused. Later in the day the cyanosis became marked and the heartbeat weak. While being lifted from the crib for a blood cell count, the child ceased breathing. Artificial respiration and stimulants were given to no avail.

Mother's Record.—The mother was twenty-four years of age and had been delivered of a normal, full-term child three years previously. At that time, complement-fixation tests for syphilis on the maternal and cord blood were negative. There is nothing to show that complement-fixation tests were done on the mother and child at the time of delivery of the infant who presented the cardiac anomaly under discussion. There was no history of abortion. Recovery from delivery was uneventful.

Autopsy.—Gross examination showed an apparently normally developed and well-nourished child, measuring 47 cm. in length. Slight general lividity and cyanosis of the nail beds were noted. The subcutaneous tissues were normally moist. The peritoneal cavity contained about 25 c.c. of clear yellow fluid that was slightly viscid. The thymus gland measured 3.5 × 3.5 × 1 cm. and presented nothing unusual.

The heart appeared to be enlarged but was not weighed because it was left attached to the lungs and great vessels. In situ, the organ measured 5 cm. in its greatest transverse diameter and 4.5 cm. in its greatest vertical diameter. The right atrium was much enlarged, whereas the left was reduced in size. The ventricular mass had no groove indicating subdivision into right and left portions, but the pattern of the coronary vessels (confirmed by dissection) showed that the right ventricle formed the major portion of the mass, and included the apex, whereas the left ventricular wall consisted of a small patch on the left dorsal side (Fig. 1).

The right and left atria received, respectively, the venae cavae and pulmonary veins in the usual manner. These vessels were of normal size. The interatrial foramen ("foramen ovale," which we think may be a persistent ostium primum) was circular and measured 0.6 cm. in diameter.

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The right ventricle was enormous; its walls averaged 0.6 cm. in thickness. The atrioventricular opening was surrounded by a large valve which showed some tendency to be divided into segments. At the upper portion of this chamber, near a point where the pulmonary artery would normally arise, was a large arterial trunk 1.1 cm. in diameter. Near its origin were three well-formed valve leaflets, of the semilunar type, arranged around a ring 3 cm. in circumference.

The left ventricle was merely a small, blind cavity, 1.8 × 0.7 × 0.1 cm., lined by smooth, normal endocardium, in the wall of the right ventricle. The mitral valve and aortic ostium were completely atretic, and the interventricular septum was normal. The mitral valve was represented by a thin imperforate membrane, approximately 0.2 cm. in diameter.

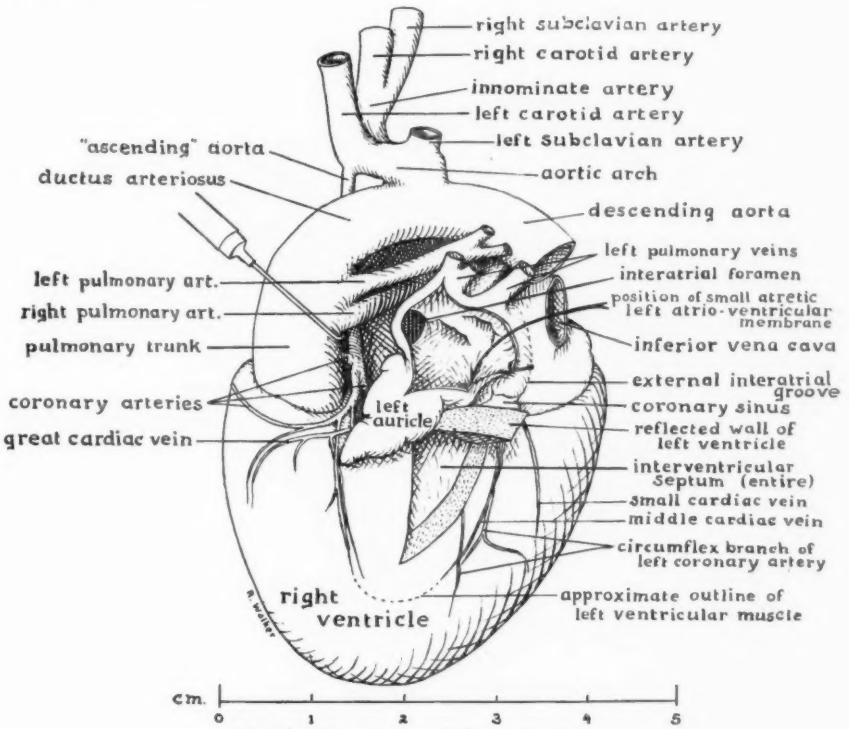

Fig. 1.—Heart viewed from the left.

The great arteries arising from the heart bore the normal fetal morphologic relations but were greatly disproportionate in size. The pulmonary trunk arose from the right ventricle in the usual manner and measured 1.1 cm. in diameter. After giving off right and left pulmonary arteries of normal size, the vessel continued to the left as the ductus arteriosus (0.8 cm. in diameter) which, after giving off a branch, continued as the descending aorta. The branch just mentioned represented the aortic arch, which gave off normal neck vessels as well as a small "ascending aorta," 0.2 cm. in diameter.

The "ascending aorta" terminated in a blind pocket, with no ridges indicating even remnants of semilunar valves. At its lowest point of patency, this rudimentary aorta gave off right and left coronary arteries which had an approximately normal distribution. The blind end, or "root," of the aorta lay, as is normal, directly opposite the commissure between two of the pulmonary cusps. In relation to the interventricular septum, however, it was misplaced, for it lay almost directly above the

right face of the septum. Thus, its wall bulged slightly into the upper corner of the right ventricle, and it was separated by some distance from the blind, functionless left ventricle.

Histologic examination of the major organs showed no remarkable changes. Particular attention was directed to the myocardium of the right and left ventricles, especially in the region of the atretic mitral and aortic valves. As far as we could ascertain, there were no signs indicating old inflammatory disease which might have accounted for atresia of either orifice. The muscle fibers were of normal size. No cellular infiltration was present.

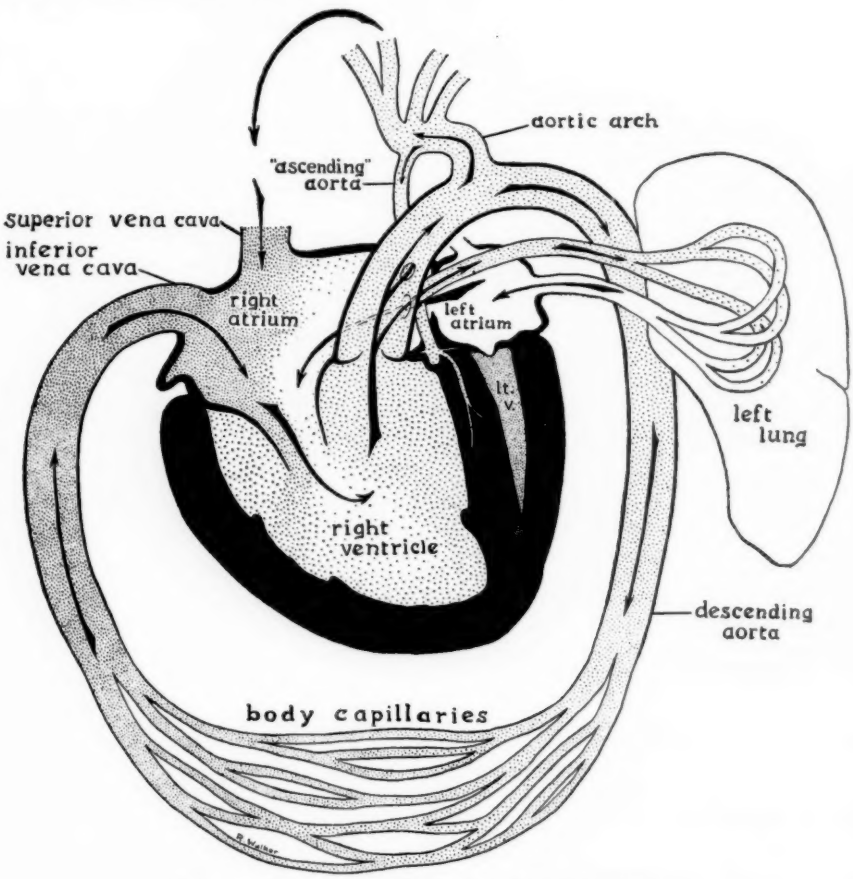

Fig. 2.—Diagram interpreting probable function.

Functionally, the structural conditions implied a complete mixing of pulmonary and systemic venous blood in the right atrium and ventricle, with distribution of equivalent, partly aerated blood to pulmonary, coronary, head, and systemic arteries (Fig. 2).

The morphologic picture consisted of atresia of all openings to the left ventricle, with hypoplasia of the left ventricle and atrium, and of the aorta, together with a wide compensatory defect in the interatrial septum, patency of the ductus arteriosus, and right-sided hyperplasia. The "ascending" aorta carried blood destined only for the coronary arteries, but in a direction opposite normal.

DISCUSSION

Although no exactly similar case has been found in the literature, the above general picture, with variations, has been presented in many cases. However, it is well to delimit the essential points and to show the bearing of the present case on the discussion as to the etiology of similar conditions. We have not attempted to review every pertinent paper, especially in the literature of the past century, but it is hoped that we have considered the most significant work of the last decades.

First, it should be clearly understood that inflammatory mitral stenosis of the adult (Lutembacher's syndrome[1]) is not comparable to fetal anomalies of development. With adult mitral stenosis there is sometimes aortic stenosis, as well. Only when there is an associated interatrial defect can the condition progress far, but in such cases there is neither the left-sided hypoplasia nor the patent ductus which are found in developmental anomalies.

Passing mention might be made of congenital pulmonary and tricuspid atresia.[2, 3] In such cases the conditions are similar to, but reversed from, the aortic and mitral atresias. There are right-sided hypoplasia, patency of the ductus and foramen ovale, and complete mixing of the blood in the enlarged left side. The variation in detail is similar to that in the series to be reviewed below, and a discussion of the etiology would probably be similar, i.e., it is to be expected that any check of flow through the right ventricle at an early stage, whether as the result of inflammatory disease or of misplacement of a septum, and whether the tricuspid or pulmonary valve was primarily involved, would entail the consequences observed.

Again, we would merely note the intermediate cases[4*, 5] in which aortic atresia or stenosis is associated with transposition of the arteries and right-sided hypoplasia, so that the results are functionally similar to ours. The case of Mills[6] seems to approximate this condition, although the ambiguity of his description leaves doubt as to whether this heart belongs here or in the main series reviewed later.

Certain reports of cases otherwise similar to ours describe a single ventricle, i.e., either absence of the left ventricle or absence of the interventricular septum. In some cases this may be so, but certain descriptions[7-12] leave a little doubt as to whether the authors may have overlooked a rudimentary cavity "imbedded" in the wall. We feel freer to make the suggestion because we ourselves made this error at first, and the possibility of error has been emphasized before.[3, 13, 14] Of the descriptions of similar "trilocular" hearts, only those of Monserrat[15] and Dudzus[16] give convincing evidence that not more than one ventricular cavity was present. Hastings'[17] description leaves some doubt, but in a personal communication he assures us that in his case, also, a systematic search was made. Such cases may, of course, be functionally similar to those with a blind left ventricle.

*Pages 181-182.

The main series to be considered here extends somewhat beyond the narrower limits of the conditions represented by our own case, and includes cases of aortic and mitral stenosis, as well as other variants which may throw light on some aspects of the problem.

In the cases reviewed, the condition of the interventricular septum varies from certain absence[15] and doubtful absence, through those with obvious defects and those with a mere cleft,[18] to cases like ours, in which the septum was normal.[19-22] In Donnally's[23] case, which was misapprehended by Abbott and Dawson,[4] the septum was also complete. When the septum is adequately indicated, it varies considerably in position relative to the two ventricles, as well as to the great arteries. In the case of Schrader,[24] for instance, the anomaly was apparently of much later origin; the ventricles were more nearly of the same size, and the smaller left ventricle still reached to the apex. In all the other cases the large right ventricle formed the apex, and the septum was usually convex to the left. In Philpott's[20] case, however, the large right ventricle curved around the small left chamber, even more than in the normal heart. It is obvious that, if the left ventricle is much reduced, there will not be room for mitral and aortic valves of normal size and position. Some cases appear to be like ours in apparent displacement of the septum relative to the aortic or mitral ostia. These would almost surely include any in which a blind left ventricle may have been overlooked, but in which aortic or mitral valves are described in relation to the (right) ventricle.[8] Usually, however, there is a general reduction of the left side of the heart, with a proportionate reduction of the (often atretic) valves, i.e., the interventricular septum clearly lies in its normal relation to the atrioventricular and arterial valves.[23, 25, 26]

The morphologic complex of which our heart is the type calls for a defect of the interatrial septum if function is to continue. The only cases reviewed in which there was no such patency are those of McIntosh,[8] in which there was compensation by abnormal communication of a pulmonary vein with the superior vena cava, and Bellet and Gouley,[27] in which the path of compensatory flow was doubtful and inadequate (patient died twelve hours after birth). Spolverini and Barbieri[28*] had an almost complete closure of the foramen ovale. They assumed that the blood returned from the lungs through the bronchial veins! Lippincott's[25] assumption that there was no flow through a patent foramen ovale fails to take cognizance of the changes from the normal pattern of circulation entailed by this complex. In one case,[22] with an aperture of only 0.2 cm., there was an associated aneurysmal bulge of the interatrial septum to the right, with thickening of the endocardium of the left side. Otherwise, there are consistent reports of considerable interatrial defects; but the size, form, and perhaps the morphologic significance of these defects are varied. In size they vary from small and perhaps inadequate openings[29, 30†, 2, 31‡] to large

*Case 7. †Case 4. ‡Case 1.

patencies, e.g., 14 mm.,[32] or even absence of the septum.[17] There is variation in shape of the foramen from a smooth, single hole, to a pair of holes[24] or even multiple openings.[14, 15]

The term "foramen ovale" is loosely used for any interatrial opening, regardless of the developmental relations. Perhaps most of the cases reported are examples of true ostium secundum, but our own case suggests persistence of the ostium primum. In such cases the opening is close against the atrioventricular (cushion) septum anteriorly, so that there is no inferior or anterior limbus of the fossa, aside from the atrial floor and anterior wall. The rather wide fossa is about two-thirds closed by a crescentic membrane growing from the superior and posterior sides. The only description in this series which closely approximates ours is that of Sprenkel.[18] If our diagnosis of ostium primum is correct, it would imply an early genesis of the defect.

The condition of the mitral valve varies from complete atresia[11, 14, 18] through stenosis with thickened edges[23, 30*] through a condition with tiny, but well-formed, cusps,[19, 21] to an essentially normal valve. In the minute valve (either atretic or stenotic), chordae may be present[9, 28†, 33] or absent.[11]

The aorta in this series most often shows atresia of the ostium, together with hypoplasia from the root as far as the arch, with coronary vessels arising just above the atresia, and so receiving blood in reverse down the ascending aorta. There is variation, however, on all of these points. The atresia may be produced by a clear membrane[26] or by a membrane with the cusps still indicated,[2, 10, 22] or there may be some distance between the blind root of the aorta and the ventricular cavity.[19] In other cases[30‡, 34, 35, 36§] there is incomplete fusion of the cusps, resulting in the persistence of a small passage. Again, in Donnally's[23] case, in spite of aortic and left-sided hypoplasia, there was only a narrowing of the mitral and aortic valves. The latter were well formed, so that the coronaries might have received enough blood by the normal route. In two cases,[8, 11] only one coronary artery, the left, was found. In two others[7, 37] the left coronary artery came from the pulmonary trunk. Gauss[19] describes closure of the aorta for 2 cm., with a common coronary origin from the left ventricle. This was presumably not a case of ostial atresia. Ziegenspeck[38] also described obliteration of part of the ascending aorta by an organized thrombus, leaving a small chamber between this region and the atretic aortic ostium. He did not specify the origin of the coronaries which are figured. These variations of coronary origin, however, are few as compared with fifteen cases reviewed in which the condition was essentially like that in ours.

There are cases in this general series in which the ascending aorta was not extremely hypoplastic.[16, 20, 28†] The two latter, however, were not cases of aortic atresia. Further, there are two cases of additional

*Case 4. †Case 7. ‡Case 2. §Group 3, Case 12.

coarctation of the aorta at a higher level, i.e., of the isthmus[37] and of the descending aorta.[10]

In general, the variations in the neck arteries which come from the aortic arch are matters of mere detail, and need not concern us here, although Philpott,[20] who says there are no anomalous vessels in this region, gives a sketch of vessels with most peculiar relationships.

The pulmonary trunk is almost always enlarged; it gives off normal branches to the lungs (also sometimes an anomalous coronary; previously mentioned), and continues into a widely patent ductus arteriosus. Of the five cases in which the ductus was closed or inadequate, all were among children whose ages exceeded the average life span for the group, and far beyond in three,[16, 30*, 28†] i.e., thirteen months, two and one-half months, and forty days. In these three there was no aortic atresia, but Dudzus' citations of Jost[39] and Rokitansky[40] give no adequate explanation of the compatibility of an inadequate ductus with continued life.

The relation of the pulmonary to the aortic trunk varies as to the degree of "detorsion,"[11] but the exact orientation is hard to compare from one report to another, for, in these cases, it is difficult to find a common criterion for "ventral" or "left," because both the morphologically dorsal and ventral surfaces may be brought to the anatomic left by hypoplasia of the left atrium and ventricle. For instance, Wesson and Beaver,[21] in both text and figure, represent the pulmonary arteries as coming from the ventral side of the pulmonary-ductus trunk, and this seems improbable in the morphologic sense. Further, their text does not mention the reverse twist of the pulmonary artery and aorta, as shown in their Fig. 2, where the course of the aorta lies anterior to the pulmonary artery. Have they artificially twisted these vessels through more than 180°? Again, Shapiro[11] shows a left pulmonary branch in surprising relation to the small aortic trunk.

The condition of the endocardium and valves on the left side varies considerably, but the cases tend to fall into two main groups: those like ours, with smooth, unthickened endocardium; and those with considerable alteration. Some descriptions omit mention of the endocardium, but, in this series, six cases are definitely in the former group. In the latter group, the commonest condition is a white, fibrous thickening of the left ventricular endocardium,[22, 26, 27, 30‡, 32, 36§] usually involving the mitral valve remnant, and sometimes the left atrial endocardium and the aortic valve. Lippincott[25] speaks of hyaline fibrosis of the endocardium. Farber and Hubbard[30*] and Mönckeberg[34] describe yellowish, elastic fibrosis. Myocardial changes have less often been mentioned, but in Farber and Hubbard's[30] first case there was scarring, as well as fatty alteration and calcification. Roberts[33] described left-sided myocardial atrophy and fibrosis, and Rukstinat[10] described congestion

*Case 2. †Case 7. ‡Cases 1 and 4. §Group 3, Case 12.

and small hemorrhages in the left ventricular myocardium. It should be stressed that although some of these conditions may affect the ascending aorta as well, the right side of the heart is uniformly unaffected.

Abbott[41] separates the cases of antenatal aortic stenosis (or atresia) which are caused by arrest of development from those of inflammatory origin, with the stenosis limited to the valves and the ventricular septum uninvolved. In the cases here reviewed, however, both normal endocardium and fibrosis were associated with either defective or normal ventricular septa. Thus, even if fibrosis of the endocardium or valves were to be considered as evidence of previous inflammation, the above classification could not hold for all cases. Further, Abbott's[42] suggestion that the lesions are frequently syphilitic is apparently unfounded. In none of these cases were spirochetes demonstrated with metallic impregnation. Only in the case of Monserrat[15] was there a history of maternal syphilis, and here no inflammatory process was detected in the heart. In the nine other cases[11, 20, 26, 27, 30, 34, 36] in which an investigation was mentioned, regardless of the methods used, positive evidence for syphilis was lacking.

Although some of the above conditions may have been of inflammatory origin, especially those involving the myocardium, it is doubtful whether mere endocardial fibrosis or thickening of the valves is a true indication. Gross, in discussing Baggenstoss'[29] case, has emphasized the absence of critical histologic evidence, even when sought, in most cases in which fetal endocarditis was assumed. For a fuller discussion of the problem, we refer the reader to the papers of Loeser,[26] Bellet and Gouley,[27] and Farber and Hubbard.[30]

The age at death in this group has a fairly smooth skew probability curve, with the mode at three days. The eight cases which scatter from eighteen days to twenty-one months, however, raise questions which cannot at present be answered. In two of these[16, 28*] there were a patent aortic valve, an inadequate ductus, and a common ventricle. It is difficult to see how this structural pattern gives any functional advantage over that in the other cases, for in both the blood must have been completely mixed; unless, one might assume a special extension of Sabatier's theory of functional segregation of the streams of blood, which has been so well proved for the normal fetal circulation by the Barcroft school[43] and others. Three cases[35, 44†] are too briefly described to indicate any reason for extended life, but there may have been some flow through the left ventricle. The same may be true of the case of Farber and Hubbard.[30‡] Two other cases[8, 15] in which death occurred at five weeks and three months, respectively, do not seem to be essentially different from the major series functionally, except for slight aortic patency in the former. The hypothesis of Roberts[33] that the length of life in these cases is proportional to the size of the interatrial

*Case 7. †Cases 2 and 3. ‡Case 2.

opening may be a fair generalization. The case of von Haam and Hartwell[32] fits this, with an opening 14 mm. in diameter and a survival period of twelve days. An outstanding recent exception was Wiglesworth's[22] case, with an opening only 2 mm. in diameter, but survival for eighteen days. It would seem, however, that with the characteristic pattern of complete stoppage of flow through the left ventricle, and complete mixing of blood in the right atrium, ventricle, and pulmonary trunk, even with adequate patency of the interatrial septum and the ductus, the expectation of life is not more than a week. Although dyspnea and cyanosis are characteristic, they are far from uniform from the time of birth.

In brief, this morphologic complex may be associated with indirect evidence of early inflammation, but more often is not. In the latter cases, at least, one should look for some early distortion of development. In our case we suspect that a misplacement of the interventricular septum, blocking the aortic ostium, was the primary defect. However, any influence which would check the flow through the mitral or aortic valves at an early enough stage might result in left-sided hypoplasia and atrophy and fusion of the valve cusps on the left. Mönckeberg[13] formulated a hypothesis of asymmetric formation of the truncus septum, resulting in a small aorta with reduced flow. But in almost all of these cases, when the rudiments of aortic cusps are visible, there is an even, triradiate pattern like that in the enlarged pulmonary valve. Even a "bicuspid" aortic valve[8] is caused by fusion of two of the three cusps. Evidently the septum has generally subdivided the ostium equally, and asymmetry developed later.

The variation in pattern is considerable; all cases show some deviation in detail from the general picture. Mönckeberg[13] described the complex as cor pseudotriloculare, with rudimentary left ventricle and atresia of the aortic ostium and mitral valve. Two of his briefly described cases and two others[14, 18] approach ours closely except for an interventricular defect. Otherwise, one of Mönckeberg's cases and ours seem to stand as close to the general condition as any yet described; we would call this condition complete closure of the left ventricle by aortic and mitral atresia, with left-sided and aortic hypoplasia, compensating interatrial and ductus patencies, and without evidence of early inflammation.

SUMMARY

A case of congenital mitral and aortic atresia, associated with hypoplasia of the left atrium and ventricle and compensating patencies of the interatrial foramen and ductus arteriosus, is described. The anomaly is attributed to a developmental misplacement of the interventricular septum. No evidence was found to indicate an inflammatory cause for the defect.

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THE EFFECT OF OXYGEN ON THE ELECTROCARDIOGRAMS OF CYANOTIC PATIENTS

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EXPERIMENTALLY induced anoxemia is known to produce alterations in the RS-T segments and T waves of the electrocardiograms of patients with coronary insufficiency.[1-5] It was believed that the administration of oxygen to patients with myocardial anoxia, caused either by coronary insufficiency or generalized anoxemia, might produce converse alterations of these deflections. Although superficial anoxia, as manifested by cyanosis, is not necessarily an index of myocardial anoxia, it seems reasonable to assume that, when cardiac insufficiency or a recent coronary occlusion is the underlying cyanosis-producing factor, at least some degree of cardiac anoxia is present. Consequently, an investigation has been made of the effects of oxygen inhalation on the electrocardiograms of cyanotic patients.

Forty-two cyanotic patients whose anoxia-producing factor was cardiac insufficiency, recent coronary occlusion, a pulmonary lesion, or a combination of these, and twenty noncyanotic controls, ten with heart disease and ten without, were chosen for this study. With the development of cyanosis (usually on admission to the hospital), oxygen was administered by the nasal route at the rate of ten liters per minute for one-half hour. Electrocardiograms were recorded before, and at the end of, the period of inhalation. The oxygen was then discontinued when the patient's condition permitted (eight patients were considered too critically ill to justify its discontinuation). Thirty minutes later a third control electrocardiogram was taken; this served to prevent mistaking progressive alterations, especially those associated with recent coronary occlusion, for alterations produced by oxygen therapy. The position of the precordial electrode was carefully marked, so that it could be exactly replaced for recording successive tracings. The limb electrodes were left in place. In this manner, alterations produced by varying the location of the electrode were eliminated.

After having compensated for the slight differences in standardization, these tracings were compared, and only those alterations in the second electrocardiogram which disappeared in the third and measured 0.5 millimeter or more in amplitude were considered significant.

OBSERVATIONS

Among the forty-two cyanotic patients there were thirty-three men and nine women. Their ages ranged from thirty-two years to seventy-four years, and averaged fifty-six years. They were classified in four groups, according to the factor which produced the cyanosis: (1) those with recent coronary occlusion, (2) those with cardiac insufficiency with-

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out recent coronary occlusion, (3) those with a pulmonary cyanosis-producing lesion, and (4) those with both cardiac insufficiency and a pulmonary lesion. Their electrocardiograms varied considerably in configuration. Six patients had normal tracings; twenty had electrocardiograms with evidence of varying degrees of myocardial disease, indefinite in character; eight had the electrocardiographic pattern of recent myocardial infarction; and six had bundle branch block.

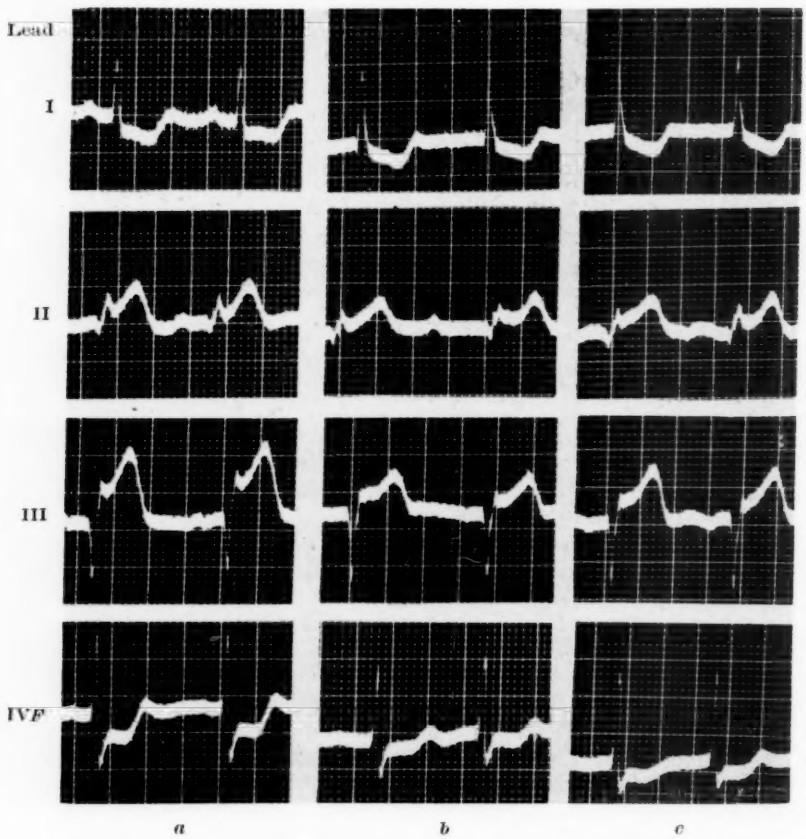

Fig. 1.—Case 42. Electrocardiograms showing the configuration indicative of posterior wall infarction, recorded (*a*) before oxygen administration, (*b*) after one-half hour of oxygen inhalation, and (*c*) one-half hour after oxygen therapy had been discontinued. Significant alterations are found in Leads II, III, and IV*F*.

The observations which were made on the electrocardiograms of these forty-two patients follow:

1. Alterations were noted in the tracings of twenty-nine patients.
2. These changes were limited to elevation or depression of the RS-T segments and the T waves.
3. The greatest alterations appeared in the T waves, particularly those of Lead IV*F*.
4. The greatest RS-T segment deviation measured 1.5 millimeters, whereas the greatest T-wave change measured 4.0 millimeters.

5. These alterations varied in direction and extent and did not necessarily, as one might expect, show a reversion toward normal, even in those electrocardiograms with a configuration diagnostic of myocardial infarction.

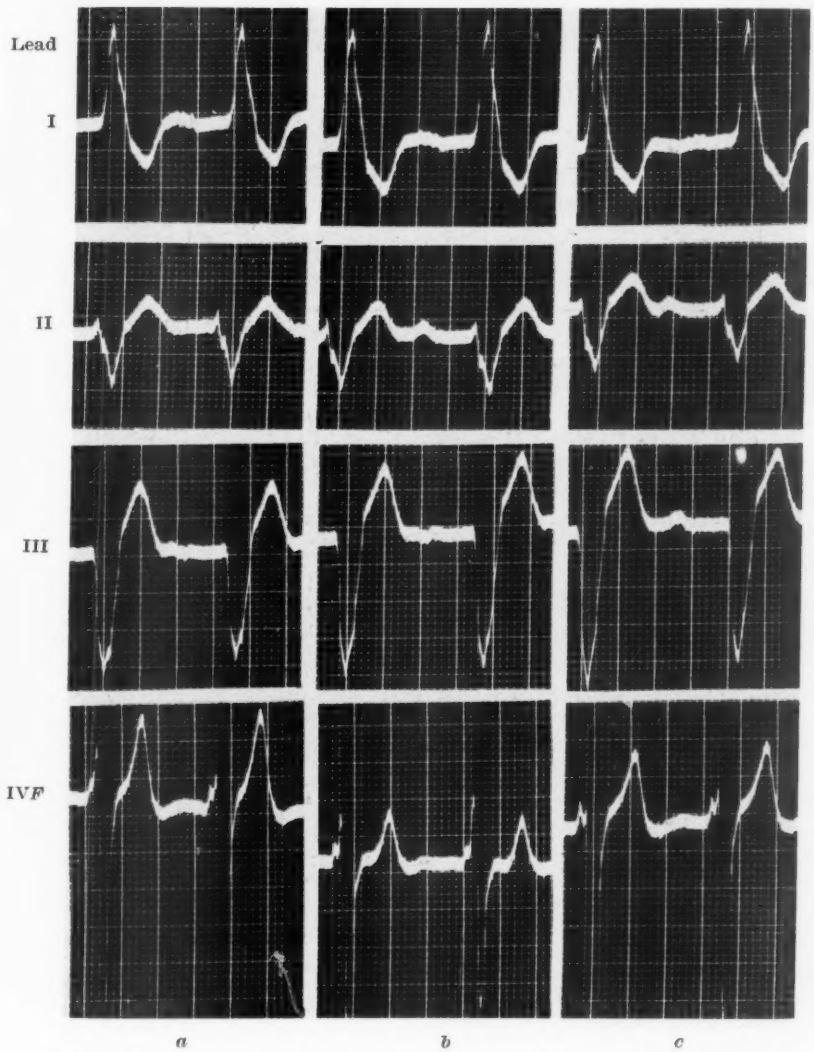

Fig. 2.—Case 36. Electrocardiograms with the configuration of left bundle branch block, recorded (*a*) before oxygen administration, (*b*) after one-half hour of oxygen inhalation, and (*c*) one-half hour after oxygen therapy had been discontinued. Significant alterations are found in Lead IV*F*.

6. RS-T segment alterations were found in the tracings of thirteen patients, and five of these had changes in more than one lead. Three-fourths of the alterations were directed toward the isoelectric line, and one-fourth away from it.

TABLE I

THE EFFECT OF OXYGEN ON THE ELECTROCARDIOGRAMS OF CYANOTIC PATIENTS

NO.	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIFICANT ALTERATIONS
1	69	Coronary occlusion Diabetes mellitus	Myocardial infarction	Slight	Improved	RSR	+
2	57	Coronary occlusion Hypertensive card.—vas. dis.	Myocardial infarction	Slight	Relieved	RSR	+
3	47	Coronary occlusion Hypertensive card.—vas. dis. Cardiac insufficiency	Myocardial infarction	Moderate	Improved	RSR	+
4	60	Coronary occlusion Diabetes mellitus	Myocardial infarction	Slight	Relieved	RSR	+
5	48	Rheumatic heart disease Cardiac insufficiency	Vent. myocard. dis.	Slight	Relieved	RSR	0
6	57	Rheumatic heart disease Cardiac insufficiency Pulmonary infarction	Vent. myocard. dis.	Marked	Improved	AF	+
7	32	Lobar Pneumonia Acute pericarditis	Vent. myocard. dis.	Moderate	Improved	RSR	+
8	60	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+
9	61	Bronchopneumonia Diabetes mellitus	Vent. myocard. dis.*	Marked	Relieved	RSR	0
10	60	Hypertensive card.—vas. dis. Cardiac insufficiency Diabetes mellitus	Left bundle branch block	Marked	Improved	RSR	+
11	62	Coronary occlusion Hypertensive card.—vas. dis.	No abnormalities	Moderate	Improved	RSR	+
12	57	Rheumatic heart disease Cardiac insufficiency	Vent. myocard. dis.	Marked	Improved	RSR	+
13	54	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+
14	73	Bronchopneumonia	Vent. myocard. dis.*	Marked	Relieved	RSR	0
15	45	Atelectasis Carcinoma of lung	Vent. myocard. dis.*	Marked	Improved	RSR	+
16	49	Hypertensive card.—vas. dis. Cardiac insufficiency Bronchopneumonia Bronchial asthma	Vent. myocard. dis.	Marked	Improved	RSR	+
17	57	Lobar pneumonia Empyema Hypertensive card.—vas. dis.	Left bundle branch block	Marked	Relieved	RSR	+

*A clinical diagnosis of heart disease has not been made in these cases, despite the finding of electrocardiographic abnormalities, because these abnormalities were slight, they were present in older individuals, in whom myocardial fibrosis is common, and they were not associated with any other clinical evidence of heart disease.

TABLE I—CONT'D

NO.	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIFICANT ALTERATIONS
18	51	Lobar pneumonia Tertiary syphilis	No abnormalities	Marked	Improved	RSR	+
19	51	Coronary occlusion Syphilitic heart disease Cardiac insufficiency	Vent. myocard. dis. Digitalis	Marked	Relieved	RSR	+
20	74	Asthmatic bronchitis	Vent. myocard. dis.*	Marked	Relieved	RSR	+
21	65	Hypertensive card.—vas. dis. Cardiac insufficiency Diabetes mellitus	Vent. myocard. dis.	Moderate	Relieved	AF	+
22	65	Hypertensive card.—vas. dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Improved	AF	0
23	36	Coronary occlusion	Myocardial infarction	Slight	Improved	RSR	+
24	59	Lobar pneumonia	No abnormalities	Marked	Improved	RSR	0
25	35	Hypertensive card.—vas. dis. Cardiac insufficiency Uremia	No abnormalities	Marked	Improved	RSR	0
26	53	Bronchopneumonia	Vent. myocard. dis.*	Marked	Improved	RSR	+
27	65	Coronary occlusion	Right bundle branch block	Marked	Improved	Idiovent.	+
28	54	Coronary occlusion	Vent. tachycardia	Moderate	Relieved	Vent. Tach.	+
29	54	Arteriosclerotic heart dis. Syphilis Lobar pneumonia	No abnormalities	Marked	Relieved	RSR	0
30	53	Arteriosclerotic heart dis. Cardiac insufficiency	Aur. tachycardia	Marked	Relieved	Aur. Tach.	0
31	62	Rheumatic heart disease Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	AF	0
32	65	Arteriosclerotic heart dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	AF	0
33	61	Coronary occlusion	Right bundle branch block	Marked	Improved	RSR	+
34	57	Arteriosclerotic heart dis. Hypertensive card.—vas. dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	RSR	0
35	66	Lobar pneumonia	Vent. myocard. dis.*	Moderate	Relieved	RSR	0

TABLE I—CONT'D

NO.	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIFICANT ALTERATIONS
36	74	Arteriosclerotic heart dis. Hypertensive card.—vas. dis. Cardiac insufficiency	Left bundle branch block	Moderate	Improved	RSR	+
37	55	Arteriosclerotic heart dis. Hypertensive card.—vas. dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Improved	Aur. Flut.	+
38	54	Thrombosis of heart Bronchopneumonia	Vent. myocard. dis.	Marked	Relieved	RSR	+
39	69	Bronchial asthma Emphysema Cor. pulmonale Cardiac insufficiency	No abnormalities	Marked	Improved	RSR	+
40	69	Syphilitic heart disease Brochopneumonia Cardiac insufficiency	Left bundle branch block	Moderate	Relieved	RSR	+
41	54	Coronary occlusion	Vent. myocard. dis.	Marked	Relieved	RSR	+
42	56	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+

7. T-wave alterations were noted in the tracings of twenty-six patients, and ten of these had changes in more than one lead. One-half of these alterations represented an increase in positivity or a decrease in negativity, whereas the other half showed a decrease in positivity or an increase in negativity.

8. Alterations were found in the tracings of all of the fourteen patients with recent coronary occlusion.* Fourteen RS-T segment alterations were found in seven cases (five had alterations in more than one lead); the greatest change in amplitude was 1.5 millimeters, and the average was 0.7 millimeter. Twenty-one T-wave changes were present in twelve cases (five had changes in more than one lead); the greatest alteration in amplitude measured 3.0 millimeters, and the average was 1.1 millimeters.

9. Alterations were found in the tracings of five of the twelve patients with cardiac insufficiency without recent coronary occlusion. RS-T segment alterations in one lead were found in two cases; one measured 1.5 millimeters in amplitude, and the other, 0.5 millimeter. T-wave alterations in one lead were present in four cases; the greatest measured 4.0 millimeters in amplitude, and the average was 1.5 millimeters.

10. Alterations were found in the tracings of three of the eight patients whose cyanosis-producing factor was a pulmonary lesion. Only

*The admission electrocardiograms (used in this study) of six of these patients were not diagnostic of myocardial infarction, but serial tracings, together with other clinical and laboratory data, proved to be convincing evidence of recent coronary occlusion.

one RS-T segment change was present in this group; it measured 0.5 millimeter in amplitude. Six T-wave alterations were present in three cases (two patients had changes in more than one lead); the greatest measured 1.0 millimeter in amplitude, and the average was 0.6 millimeter.

11. Alterations were found in the tracings of seven of the eight patients whose cyanosis was produced by a combination of cardiac insufficiency and a pulmonary lesion. RS-T segment alterations in one lead were found in two cases; one measured 1.0 millimeter in amplitude, and the other, 0.5 millimeter. Twelve T-wave alterations were present in seven cases (three patients had changes in more than one lead); the greatest measured 2.7 millimeters in amplitude, and the average was 0.9 millimeter.

12. There was no correlation either between the degree of cyanosis and the number or degree of the electrocardiographic changes, or between the extent of the clearing of cyanosis produced by oxygen and these alterations.

13. There were alterations in all of the six cases in which the electrocardiograms conformed to the pattern of bundle branch block.

14. No alterations were observed in any RS-T segment whose take-off was isoelectric.

15. The presence or absence of electrocardiographic modifications bore no apparent relation to prognosis.

The noncyanotic controls, composed of sixteen men and four women, ranged in age from twenty-nine years to sixty-eight years; the average was 44.7 years. They were divided into two groups, those with clinical and laboratory evidence of compensated heart disease, and those without any evidence of cardiac abnormalities. The electrocardiograms of the compensated cardiacs showed evidence of myocardial damage in all but one case, whereas the tracings of the patients without heart disease were all normal.

The electrocardiograms taken on the noncyanotic controls revealed:

1. No alterations in the tracings of the ten compensated cardiac patients.

2. An elevation of the T wave in three of the ten patients with no evidence of heart disease, and an elevation of the RS-T segment in one of these three.

3. No relation between the age of the patient and the changes produced in either the cyanotic or the noncyanotic group.

DISCUSSION

From these observations it becomes apparent that inhalation of oxygen altered the cardiac physiology of 69 per cent of these cyanotic patients in such a manner and to such an extent as to be demonstrable in serial electrocardiograms. Among the noncyanotic controls, however,

Table II

An Analysis of the RS-T Segments, the T Waves, and Their Corresponding Alterations in the Electrocardiograms of the Cyanotic Patients Whose Tracings Showed Significant Deflections

Case No.	RS-T segments								T waves							
	Amplitude of original deflection*				Alteration produced by oxygen*				Amplitude of original deflection*				Alteration produced by oxygen*			
	Lead				Lead				Lead				Lead			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
1	0	−1.0	−1.0	+1.0	0	0	+0.5	−0.5	−1.5	+1.0	+2.5	−4.0	0	0	0	0
2	−0.5	+1.5	+1.5	−2.0	0	−0.5	−0.5	+1.0	+1.1	+3.5	+4.0	−5.0	+0.8	−1.4	−3.0	+3.0
3	0	0	0	+7.5	0	0	0	0	−0.5	−1.0	−0.5	−2.0	0	+0.5	0	+1.5
4	+1.5	0	−1.0	+8.0	0	0	0	+1.5	+1.5	+1.0	+1.0	+9.2	0	0	0	+1.7
6	+0.7	−0.7	−1.0	+2.0	0	0	0	−1.0	+0.9	−0.5	−1.5	+4.0	0	0	0	−1.0
7	+1.5	+1.0	−0.2	+1.0	+0.5	0	0	0	+5.0	+4.5	−0.5	+7.0	0	+0.5	0	0
8	−1.0	+1.0	+1.5	−2.2	0	0	0	0	+1.8	−1.5	−3.2	+7.5	0	0	−0.5	0
10	0	+0.5	+1.0	+4.0	0	0	0	−0.5	+1.0	+3.0	+2.5	+12.0	0	0	0	0
11	0	0	+0.5	0	0	0	0	0	+1.5	+1.5	0	+3.5	0	0	0	+0.5
12	0	−0.3	−0.5	+0.5	0	0	0	0	+1.0	−1.2	−1.5	+2.0	+0.5	0	0	0
13	+1.5	+0.8	−0.5	+4.5	0	0	0	+0.5	+1.8	+2.0	+1.0	+7.0	0	0	0	0
15	0	0	0	+0.5	0	0	0	0	+1.0	+2.0	+1.5	+1.5	−0.5	−0.6	0	0
16	0	0	0	−1.0	0	0	0	+0.5	+1.5	+2.0	+1.5	+0.5	−0.5	−0.8	−1.0	+0.5
17	+1.0	0	0	+2.0	0	0	0	0	+3.8	+1.8	−2.0	+9.0	0	0	+1.0	−2.7
19		−1.0		+0.5	0	0	0	−0.5		−2.5		+3.0		0		−1.0
20	−1.0	−2.0	−0.5	−2.0	0	0	0	0	+0.5			+3.0	−0.5			0
21	0	0	0	0	0	0	0	0	+0.5	+1.0	+1.5	+0.5	0	0	0	−1.0
23	0	+0.3	+0.7	−1.0	0	0	0	0	+2.0	+2.0	0	+4.0	0	0	0	+1.0
26	0	0	0	0	0	0	0	0	+1.5	+1.5	0	0	+0.5	+0.5	0	+1.0
27	0	−0.5	−0.7	+5.9	0	0	−0.8	+0.5	+1.2	−2.5	−3.0	+8.5	0	+0.5	0	0
28	+4.0	−1.0	0	+2.5	−0.5	0	0	−1.0	+4.5	+1.2	−2.8	+4.5	−0.5	0	0	+0.5
33	−0.5	+0.5	+0.6	+1.0	0	0	0	0	+1.2	−2.2	−3.0	−1.0	+0.5	+1.2	+1.5	0
36	−3.0	+0.5	+3.5	+1.5	0	0	0	−1.5	−5.5	+3.5	+8.5	+12.5	0	0	0	−4.0
37	+0.3	+0.2	−0.3	+0.5	0	0	0	0	+1.0	+1.0	+1.0	+1.0	0	0	0	+0.5
38	0	0	−0.8	+1.0	0	0	0	0	+0.9	+1.5	+1.2	+1.6	0	0	0	+0.6
39	+0.5	+0.5	+0.3	+0.5	0	0	0	0	+1.6	+1.5	−0.5	+4.1	0	0	0	+0.7
40	0	0	0	0	0	0	0	0	+1.8	+2.0	+1.2	−1.9	0	−0.8	−0.8	0
41	−0.5	−1.5	0	+2.0	0	0	0	0	−1.0	−2.2	−0.2	+8.2	0	0	−0.7	0
42	−1.3	+1.5	+4.0	−3.7	0	0	−0.5	+0.6	−2.7	+5.5	+9.2	−3.8	0	−0.8	−1.8	+1.5

*Measured in millimeters.

TABLE III

AN ANALYSIS OF THE RS-T SEGMENTS, THE T WAVES, AND THEIR CORRESPONDING ALTERATIONS IN THE ELECTROCARDIOGRAMS OF THE NORMAL, NONCYANOTIC SUBJECTS WHOSE TRACINGS SHOWED SIGNIFICANT DEFLECTIONS

CASE NO.	RS-T SEGMENTS								T WAVES							
	AMPLITUDE OF ORIGINAL DEFLECTION*				ALTERATION PRODUCED BY OXYGEN*				AMPLITUDE OF ORIGINAL DEFLECTION*				ALTERATION PRODUCED BY OXYGEN*			
	LEAD				LEAD				LEAD				LEAD			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
1	+0.5	+1.0	+0.5	0	0	0	0	0	+2.0	+3.2	+1.2	+4.2	0	0	0	+0.8
4	+0.2	+0.3	+0.2	+0.5	0	0	0	+0.5	+1.2	+0.7	−0.3	+3.0	0	+0.7	0	+0.8
10	+0.2	0	0	+0.3	0	0	0	0	+0.5	+0.8	+0.2	+2.0	0	0	0	+0.5

*Measured in millimeters.

such modifications were present in only 15 per cent of the cases. That these alterations were not proportional to the degree of cyanosis or to the extent of its improvement with oxygen therapy is understandable, for it is known that there is no constant relationship between peripheral and coronary anoxemia.

It is notable that frequent varying alterations, in either a positive or a negative direction, were found in abnormal electrocardiograms, whereas only a few changes, all in the direction of increased positivity, were found in normal tracings. This observation suggests that the production, by oxygen, of physiologic changes in the myocardium sufficient to alter the electrocardiogram depends largely upon the presence and the extent of myocardial damage. The fact that electrocardiographic modifications were observed in every case of recent coronary occlusion and in every case of bundle branch block offers further support to such an hypothesis.

It was observed that the alterations produced by inhaling oxygen frequently did not show the expected reversion toward normal, particularly in the cases of recent coronary occlusion. Thus, depression of an RS-T segment or an increase in the negativity of a T wave, ordinarily indicative of myocardial disease or toxicity, may also be produced by the therapeutic agent, oxygen. The explanation for this unexpected, as well as the expected, response to the inhalation of oxygen may possibly be found in the varying degree of oxygenation of normal as compared with damaged myocardium. On the one hand, an increase in oxygenation may be greater in normal areas than in abnormal areas of the myocardium. Such a combination of circumstances would accentuate the abnormalities of the electrocardiogram, for it would increase already existing differences. An inverted T wave, for example, would be further depressed. On the other hand, the increase in oxygenation may be greater in damaged areas than in normal areas of the myocardium. In this case the electrocardiographic abnormalities would be decreased, and thus an inverted T wave would tend to right itself. The main factor governing the degree of oxygenation of normal as compared to damaged myocardium is the patency of the coronary arteries.

This study, therefore, offers further evidence in proof of the hypothesis that changes in the degree of oxygenation of the myocardium tend to produce alterations in the electrocardiogram, and that these alterations are confined to the RS-T segments and the T waves in all four leads; and it further points out that the effect of oxygen on the anoxia of a diseased heart is not expressed in the electrocardiogram by any set pattern, but rather by a variety of patterns which probably depend largely upon the state of health and oxygenation of the individual muscle bundles of the myocardium.

SUMMARY

1. Observations were made on the effect of oxygen therapy on the electrocardiograms of forty-two patients whose cyanosis-producing factor was cardiac insufficiency, recent coronary occlusion, a pulmonary lesion, or a combination of these, and twenty noncyanotic controls, ten with compensated heart disease and ten without heart disease.

2. Alterations were noted in the electrocardiograms of twenty-nine (69 per cent) cyanotic patients and in only three (15 per cent) of those of noncyanotic controls.

3. The alterations were confined to the RS-T segments and the T waves.

4. In abnormal tracings the changes were expressed by either an increase or a decrease in positivity or negativity of the deflections, whereas in normal tracings they were manifested only by an increase in positivity.

5. Alterations were noted in all fourteen cases of recent coronary occlusion and in all six cases of bundle branch block.

6. This study offers support to the hypothesis that changes in the degree of oxygenation of the myocardium tend to produce alterations in the electrocardiogram.

7. It further points out that the lack of uniformity of alterations in abnormal electrocardiograms is probably due to the varying state of health and oxygenation of the individual muscle bundles of the myocardium.

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THE USE OF HEPARIN FOR THE COMPLICATIONS WHICH FOLLOW SCLEROSING OF VARICOSE VEINS BY MASSIVE INJECTION

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IN 1938, a surgical procedure for sclerosing varicose veins by the massive injection of one dose of sodium ricinoleate was presented.[1] This procedure proved to be extremely efficient. We have found that the process is attended by one undesirable side reaction, namely, postoperative edema which lasts for a period of three to five weeks in 10 to 12 per cent of cases. This occurred in spite of every precaution to ascertain the preoperative condition of the deep venous circulation.*

In our earlier experiences, we attempted to combat this undesirable postoperative complication by mecholyl iontophoresis, plus prostigmin by subcutaneous injection, whirlpool baths, the oscillating bed with intermittent venous compression, and bandaging. Amelioration of symptoms was always obtained, but the treatment took too long. In spite of early institution of treatment, the symptoms grew in severity for two or three days before there was evidence of improvement.

In attempting to evaluate the mechanism responsible for this edema after the massive injection of sclerosing material, we found that the thrombosis which occurred at the site of the induced chemical phlebitis had a tendency to extend beyond the field in which thrombosis was desired, i.e., to the communicating veins and even the deep veins, in spite of the fact that only superficial veins were injected. Although chemical thrombosis and phlebitis are desirable in order to obliterate the varicose veins, prevention of the extending thrombosis would greatly enhance the value of the operation.

It occurred to us, therefore, that a simple method of controlling the extent of thrombosis would be to use heparin. From experimental and clinical observations we know that simple thrombosis occurs within twelve hours. Recently, an opportunity was afforded to examine veins which had been sclerosed by this method sixteen hours after injection (the patient was accidentally killed). We found that the long saphenous vein was sclerosed almost to the ankle with a firm clot. But, in addition, the communicating branches above and below the knee also showed some phlebitis (chemical), and a small amount of clot was adherent

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*Since this paper was written, another preoperative test has been used to ascertain the status of the deep venous circulation. A venogram is made by injecting 20 c.c. of diodrast (35 per cent solution) in the lesser saphenous vein at the ankle. This is done in every case of edema resulting from varicose veins (other causes ruled out), and when there is the slightest question of a previous thrombophlebitis. This procedure in detail will be published soon.

to the intima but was not completely sclerosing the vessel. The thrombosis obviously was extending. The next day our examination probably would have suggested the advisability of using heparin. In view of the fact that the clotting which follows chemical phlebitis in the treatment of varicose veins is desirable, heparinization was not instituted until twenty-four hours after injection of the sclerosing material. It is important to remember that heparin does not dissolve a thrombus but prevents further clotting and extension of the thrombosis.

PROCEDURE

Immediately after operation and injection, the legs are wrapped in elastic bandages from the toes to the knee, and the patient walks from the operating room, either to his room in the hospital or to the car or bus taking him home. During the next ten to twelve hours he is instructed to walk for ten minutes every hour until retiring. During this period, treatment of pain consists of local cold compresses with or without witch hazel and analgesics.

The following day the patient reports for examination, and certain facts regarding the status of the venous circulation are ascertained. Measurements of the legs are compared with preoperative measurements. Heparin therapy, plus the usual regimen, is instituted if the following indications are present: (1) marked swelling of the entire injected leg, with an increase in circumference of one-half inch at the ankle, one inch at the calf, and two inches at midthigh; (2) tenderness and discoloration of the skin over and about the veins; (3) sharp, cramp-like pains along veins radiating to the inguinal and lower abdominal regions; (4) impaired circulatory function in the leg, as shown by tests (Oschner-Mahorer-oscillometric, circulation time, venous pressure, increase in sedimentation time, and leucocytosis).

Heparin is given in doses of 10,000 units intravenously every four hours. It is not given by continuous infusion because the patient is confined in an oscillating bed. The clotting time is taken before each injection, and when it reaches ten to twelve minutes the heparin treatment is discontinued, but the usual treatment which is required for two or three days after cessation of pain to relieve the edema is not discontinued.

RESULTS

Fourteen patients were treated with heparin, in addition to the usual treatment. Pain was relieved in most cases four hours after the first injection of heparin, and never later than after the second injection (eight hours). Likewise, there was no evidence of increasing circulatory embarrassment after the second injection. The undesirable postoperative sequelae in all cases disappeared at the most in five days, and the patients left the hospital. This is a vast improvement over the results in twenty-nine cases with the usual routine before heparin was added

to the treatment. Without heparin, the symptoms increased in severity, regardless of treatment, for two or three days. Hospitalization for two to three weeks was necessary, and the treatment was continued thereafter for two or three weeks at the clinic before complete recovery was accomplished.

CONCLUSION

We feel that the addition of heparin to our usual regimen of treatment of the complications which follow sclerosing of varicose veins by massive injection has improved the value of the procedure because it reduces the postoperative disability, pain, and extensive destruction of the venous circulation.

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Heparin, in the form of liqualmin, and prostigmin methylsulfate were generously supplied by Roche-Organon and Hoffmann-La Roche, respectively, Nutley, New Jersey.

THE ELECTROCARDIOGRAM AFTER STANDARD EXERCISE AS A FUNCTIONAL TEST OF THE HEART

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AN OBJECTIVE test of cardiac function is of importance in distinguishing functional from organic heart disease. It is useful in diagnosis and is helpful in studying the progress of disease and the degree of physical disability. It is of particular value when other examinations of the heart are negative, i.e., physical examination, electrocardiogram, fluoroscopy, exercise tolerance test, etc.

The test to be described in this report consists of recording an electrocardiogram after a definite amount of work, standardized for the patient's age, sex, and weight.[1-4] It is essential to utilize a standard amount of work; for even healthy persons, if they exercise to excess, may have abnormal electrocardiographic responses.[5-10] It is therefore important that the exertion to which the patient is subjected will not produce abnormal electrocardiographic changes in any healthy person. This has been verified for the standard two-step test. In addition to recording the electrocardiogram after the two-step test, the patient's exercise tolerance can be measured in the ordinary way, that is, by obtaining blood pressure and pulse rate readings before and after exercise.[1, 2]

PROCEDURE AND MATERIAL

The number of climbs on the steps which the patient performs is obtained from previously prepared tables[2] based on sex, age, and weight (Tables I and II). Two steps, each nine inches high, totaling eighteen inches, are climbed a prescribed number of times by the patient in exactly one and one-half minutes. An electrocardiogram is taken immediately on cessation of the exercise and repeated three minutes and then eight minutes later, and these tracings are compared with the control tracing, made before commencing the trips on the steps. In actual performance, the electrodes are strapped on the patient's arm, left leg, and precordium (Fig. 1).

We often have the patient make double the number of trips when the standard exercise gives a negative test. That is, an hour later, or the next day, the test is repeated with twice the number of ascents in exactly three minutes. In other words, the same rate of work is continued, but twice the amount is performed. We have ascertained that the doubled two-step exercise does not result in significant electrocardiographic changes in healthy persons. Work beyond this, either by quickening the rate of climb or prolonging the period, may produce electrocardiographic alterations in normal people.[5-10]

An abnormal response in the electrocardiogram is considered to be depression of the RS-T segment of more than 0.5 mm. below the isoelectric line or an alteration

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TABLE I

STANDARD NUMBER OF ASCENTS FOR MALES*

WEIGHT (LB.)	AGE IN YEARS												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
40-49	35	36											
50-59	33	35	32										
60-69	31	33	31										
70-79	28	32	30										
80-89	26	30	29	29	29	28	27	27	26	25	25	24	23
90-99	24	29	28	28	28	27	27	26	25	25	24	23	22
100-109	22	27	27	28	28	27	26	25	25	24	23	22	22
110-119	20	26	26	27	27	26	25	25	24	23	23	22	21
120-129	18	24	25	26	27	26	25	24	23	23	22	21	20
130-139	16	23	24	25	26	25	24	23	23	22	21	20	20
140-149		21	23	24	25	24	24	23	22	21	20	20	19
150-159		20	22	24	25	24	23	22	21	20	20	19	18
160-169		18	21	23	24	23	22	22	21	20	19	18	18
170-179			20	22	23	23	22	21	20	19	18	18	17
180-189			19	21	23	22	21	20	19	19	18	17	16
190-199			18	20	22	21	21	20	19	18	17	16	15
200-209				19	21	21	20	19	18	17	16	16	15
210-219				18	21	20	19	18	17	17	16	15	14
220-229				17	20	20	19	18	17	16	15	14	13

TABLE II

STANDARD NUMBER OF ASCENTS FOR FEMALES*

WEIGHT (LB.)	AGE IN YEARS												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
40-49	35	35	33										
50-59	33	33	32										
60-69	31	32	30										
70-79	28	30	29										
80-89	26	28	28	28	28	27	26	24	23	22	21	21	20
90-99	24	27	26	27	26	25	24	23	22	22	21	20	19
100-109	22	25	25	26	26	25	24	23	22	21	20	19	18
110-119	20	23	23	25	25	24	23	22	21	20	19	18	18
120-129	18	22	22	24	24	23	22	21	20	19	19	18	17
130-139	16	20	20	23	23	22	21	20	19	19	18	17	16
140-149		18	19	22	22	21	20	19	19	18	17	16	16
150-159		17	17	21	20	20	19	19	18	17	16	16	15
160-169		15	16	20	19	19	18	18	17	16	16	15	14
170-179		13	14	19	18	18	17	17	16	16	15	14	13
180-189			13	18	17	17	17	16	16	15	14	14	13
190-199			12	17	16	16	16	15	15	14	13	13	12
200-209				16	15	15	15	14	14	13	13	12	11
210-219				15	14	14	14	13	13	13	12	11	11
220-229				14	13	13	13	13	12	12	11	11	10

*Taken from AM. HEART J. **10**: 497, 1935.

from a positive T wave to a flat or inverted T wave. Also, a change from a previously inverted T wave to a flat or upright T wave is abnormal. The RS-T depressions and T-wave inversions are the changes commonly observed. Occasionally, multiple premature beats, widening of the QRS, deep Q waves, prolongation of the P-R interval, or heart block may occur, and these are considered an abnormal response

TABLE III

INCIDENCE OF SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

	AMOUNT OF EXERCISE			
	STANDARD TWO-STEP TEST		DOUBLE STANDARD TWO-STEP TEST	
	No.	% Positive	No.	% Positive
1. Normal adults over 40 years of age	65	0	34	0
2. Patients with angina pectoris and normal control E.C.G.	54	10 (19%)	41	16 (39%)
3. Patients with angina pectoris and abnormal control E.C.G.	29	15 (52%)	15	10 (67%)
4. Patients with previous coronary occlusion and normal control E.C.G.	10	0	7	1 (14%)
5. Patients with previous coronary occlusion and abnormal control E.C.G.	43	20 (47%)	15	7 (47%)

Fig. 1.—Photograph illustrating technique of standard two-step test.

to the test. In ascertaining the level of the RS-T segment, the P-R segment is considered the isoelectric level. In this report we present the results of performing the tests on 65 normal adults over forty years of age, 83 patients with angina pectoris caused by coronary artery disease, 54 of whom had a normal control electrocardiogram, and 53 patients with previous coronary occlusion, 10 of whom had a normal control electrocardiogram (Table III).

RESULTS

Group 1, Normal Adults.—Sixty-five normal subjects, comprising 58 males and 7 females from forty to sixty-eight years of age, were chosen as controls. They were considered normal in that they appeared healthy,

had no complaints, and were engaged in regular activities. Their physical examination, electrocardiogram, teleoroentgenogram, fluoroscopic examination, roentgenkymogram, and exercise tolerance tests were entirely negative.

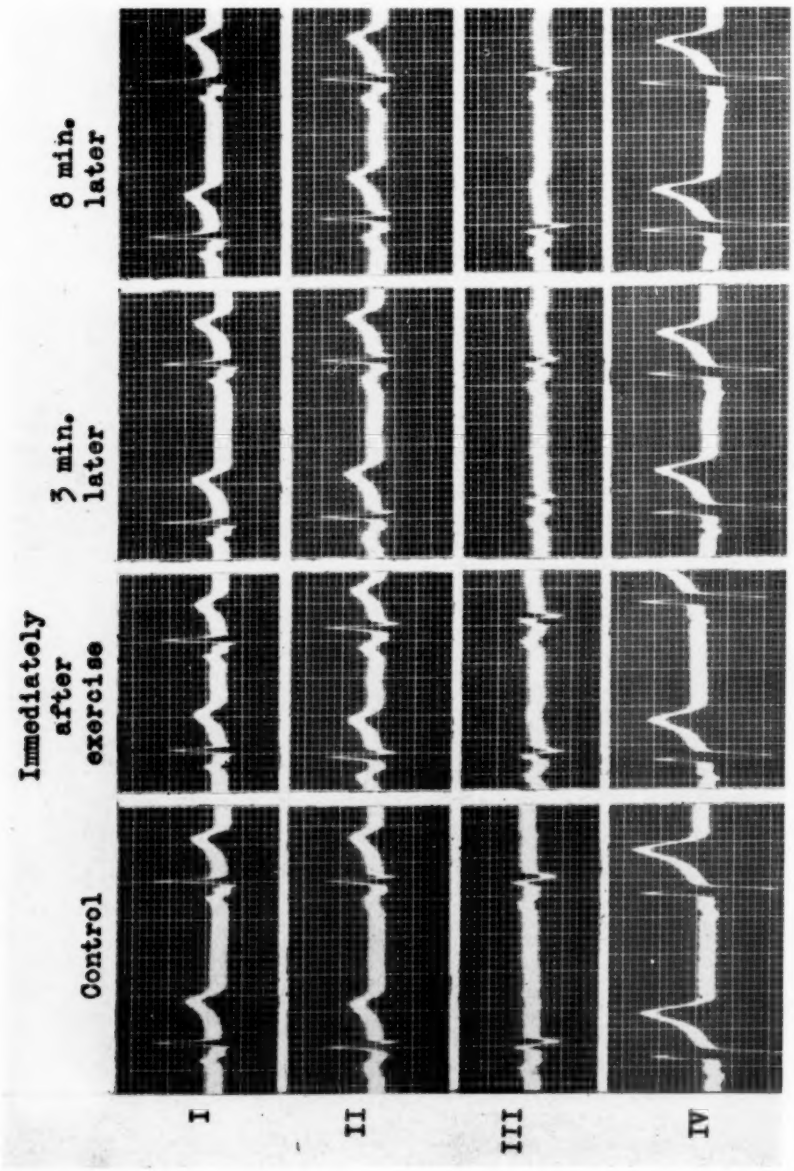

Fig. 2.—A normal man (L. H.), 47 years of age. Electrocardiograms after the double standard two-step test (42 trips in 3 minutes) show no change from the normal control record.

These 65 normal persons showed no significant changes in the electrocardiogram after the two-step exercise. In 34 instances we were able to repeat the test with double the number of climbs. In all these, too, there

was a negative response in the electrocardiogram (Table III). In not a single case of our normal series were there changes similar to those observed in the other groups. A negative test is illustrated in Fig. 2, in which are shown the electrocardiograms after a double two-step test (42 trips) on a healthy physician (L. H.), 47 years of age.

Group 2, Angina Pectoris With Normal Electrocardiogram.—This group consisted of 54 patients with angina pectoris whose electrocardiograms were normal. After the standard two-step test, 19 per cent developed significant electrocardiographic changes, and, after the double two-step test, this rose to 39 per cent (Table III). Two illustrative cases are presented.

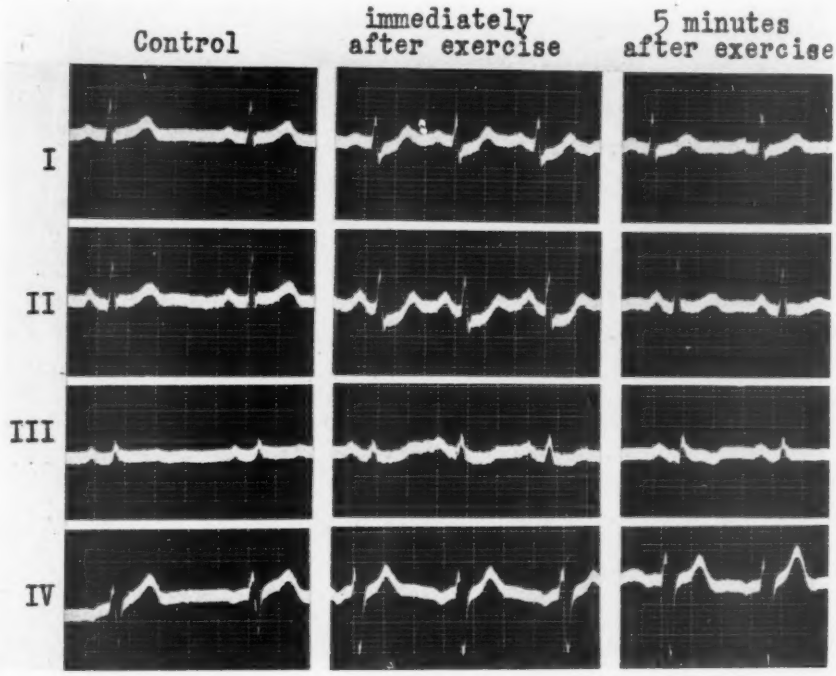

Fig. 3.*—Case 1 (M. K.). A man of 57, suffering from angina pectoris. The control electrocardiogram is normal. After the standard two-step test (20 trips in 1½ minutes) there is transient depression of the RS-T segment in all leads, particularly Leads I and II.

CASE 1 (Fig. 3).—This patient (M. K.), a man, 57 years old, was first seen December 15, 1939, because of pressure in the chest and both arms which was unrelieved by nitroglycerine. The patient weighed about 128 pounds. The heart beat was regular and the rate was 76 per minute; the heart sounds were of good quality and no murmurs were heard. The teleoroentgenogram revealed that the heart and aorta were normal in size, shape, and position. Fluoroscopic examination disclosed good cardiac contractions. The electrocardiogram was entirely normal. The patient had been operated upon for a gastric ulcer in 1930, and an exploratory operation had been performed in 1937 in a search for gastric or intestinal abnor-

*We thank the Journal of the Mount Sinai Hospital (7: 629, 1941) for permission to reproduce this illustration.

malities. Because of the persistence of pain in the chest despite the absence of objective evidence of heart disease, and because it was thought that his complaints might be reflex manifestations of gastrointestinal disease, the patient was admitted to the Mount Sinai Hospital Jan. 4, 1940, for further study.

In the hospital, also, the physical examination, teleoroentgenogram, fluoroscopic examination of the heart, and electrocardiogram were normal. Radiographic investigation of the gastrointestinal tract revealed no abnormalities. The exercise tolerance

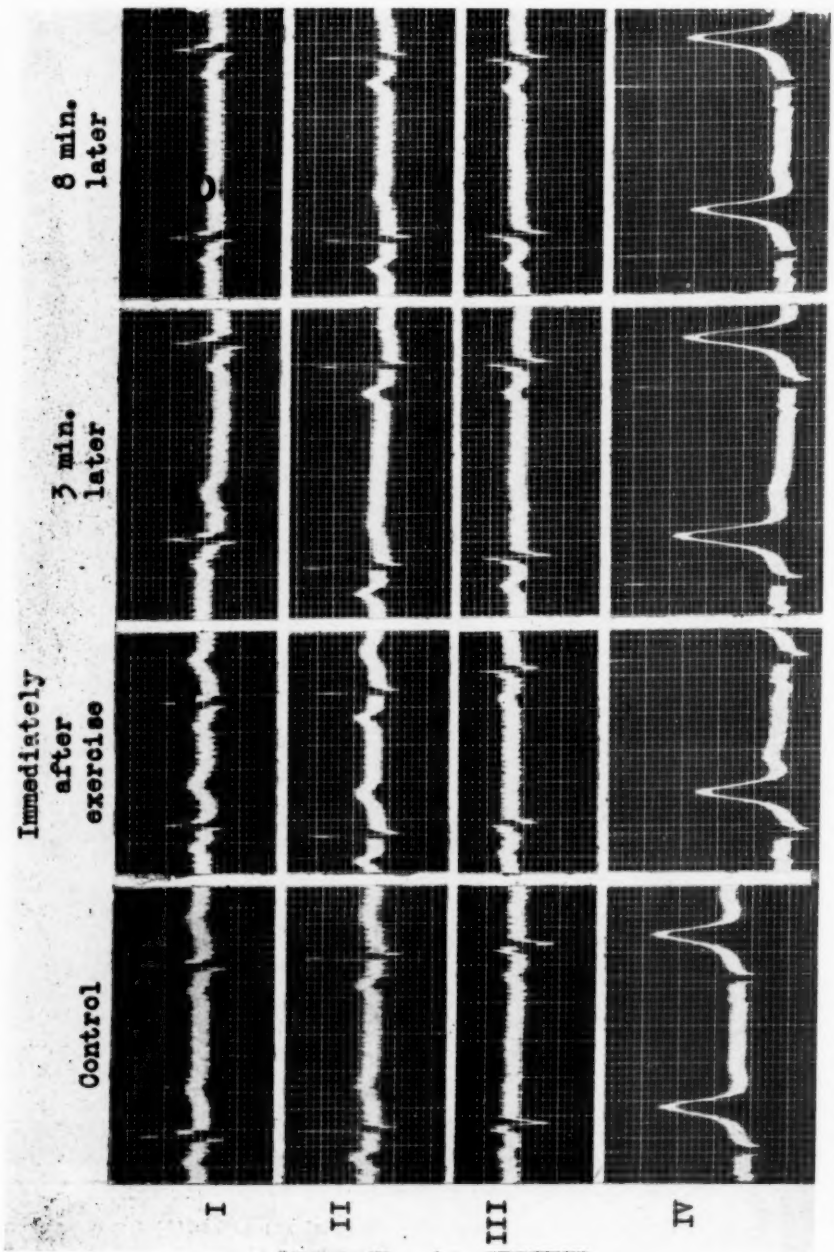

Fig. 44.—Case 2 (J. G.), male, aged 61 years. Angina pectoris for eleven years. Control electrocardiogram shows left axis deviation, small Q_1, and slight slurring of QRS. After standard two-step test (21 trips in 1½ minutes) $S\text{-}T_2$ and $S\text{-}T_4$ become depressed, T_2 low, and T_1 higher and pointed.

test, however, showed that the blood pressure and pulse rate failed to return to normal after the standard two-step exercise. Electrocardiograms after standard and double standard exercise were also definitely abnormal, in that they showed distinct depression of the RS-T segments (Fig. 3). The diagnosis of angina pectoris caused by coronary sclerosis was therefore made, and the patient was discharged

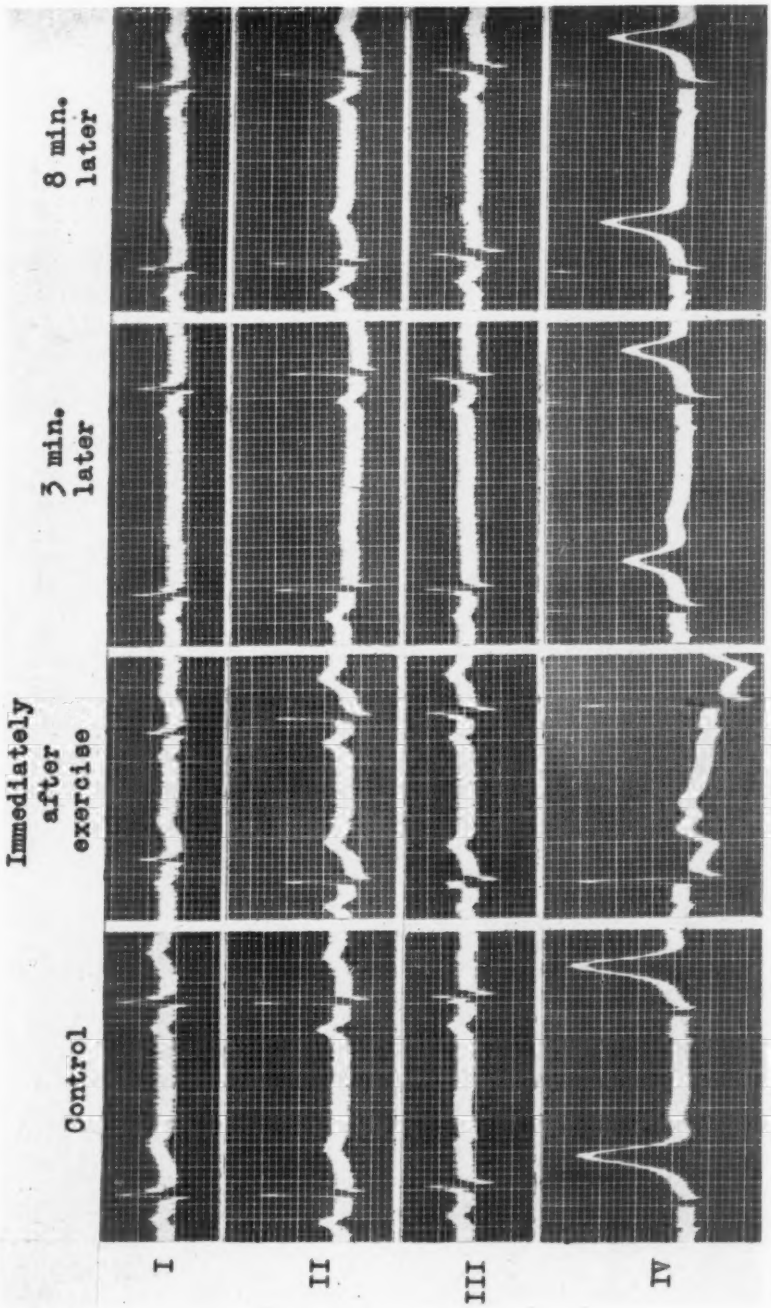

Fig. 4B.—Same case. After double standard two-step test (42 trips in 3 minutes) there is more distinct depression of S-T_2 and S-T_4; T_1 and T_4 become diphasic, and T_3 isoelectric. All the changes disappeared within 8 minutes.

Jan. 14, 1940. Aside from the reduced exercise tolerance, the appearance of significant electrocardiographic changes after standard exercise was the only objective sign of organic heart disease. This diagnosis was entirely correct, for the patient died in September, 1940, of acute coronary occlusion.

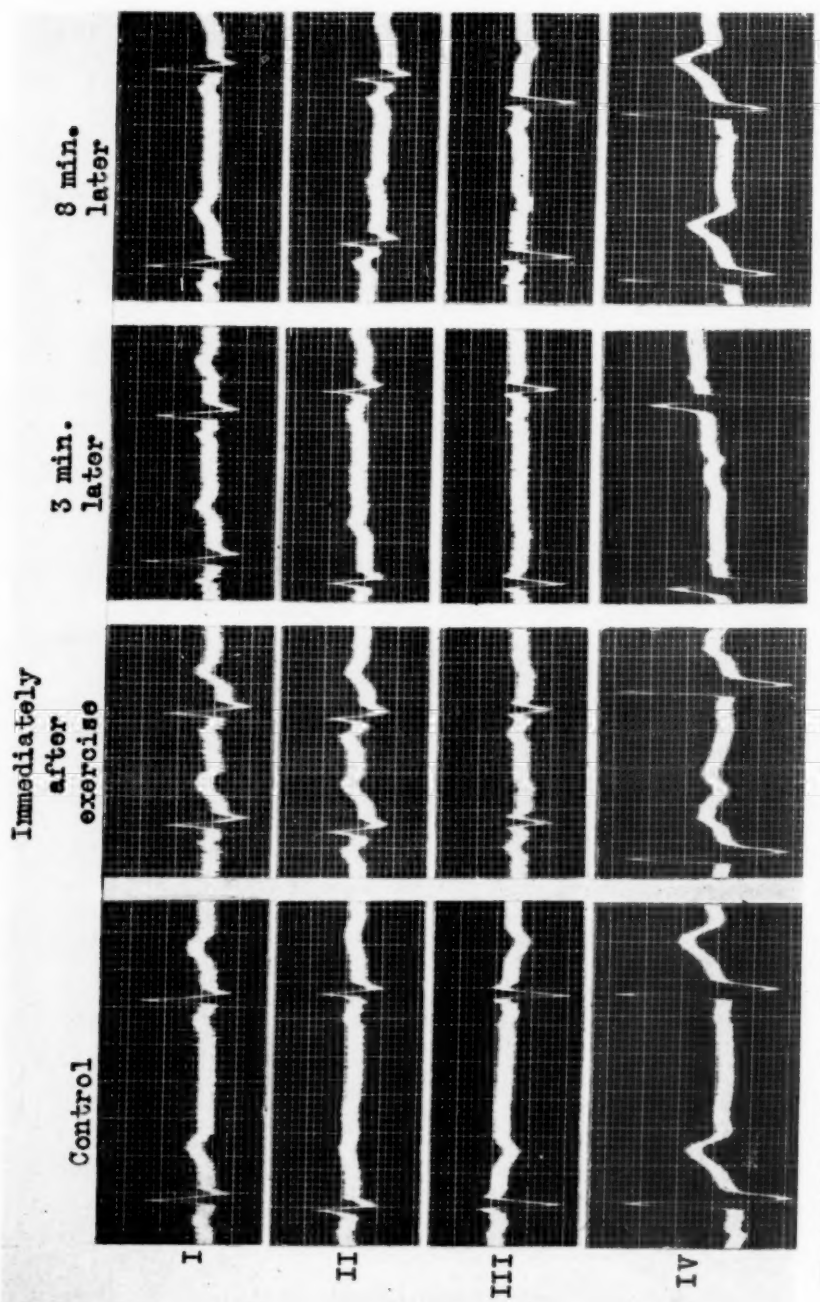

Fig. 5.—Case 3 (M. P.), a man 62 years of age, with angina pectoris. The control electrocardiogram is slightly abnormal, showing left axis deviation, slurring of QRS, a low T_2, and an inverted T_3. After the double standard two-step test (34 trips in 3 minutes) depression of the S-T segment in Leads I, II, and IV, and lowering of T_1 appear and last for several minutes.

CASE 2.—Fig. 4*A* shows the electrocardiograms of a 61-year-old man (J. G.) who, because of angina pectoris on effort for the preceding eleven years, had been forced to stop work. The heart sounds were distant and the aorta tortuous, dense, and calcified. However, the size of the heart was normal and the cardiac pulsations were of good amplitude. The electrocardiogram was essentially negative, except perhaps for the presence of a small Q_1. Immediately after 21 climbs in one and one-half minutes (Fig. 4*A*), RS-T_4 was lowered from an elevation of 1 mm. above the isoelectric line in the control record to a depression of 1 mm. below. Three minutes later T_2 became flat; eight minutes after the exercise the electrocardiogram had returned to normal. When the test was repeated with double the number of trips, i.e., 42 trips in three minutes (Fig. 4*B*), the changes in the electrocardiogram were much more marked. The RS-T segment in both Leads II and III were depressed, and T_4 was inverted immediately after exercise. Three minutes later T_1 was slightly inverted and T_2 flat, but the RS-T abnormalities had disappeared. Eight minutes later the electrocardiogram was again entirely normal. In this case also, therefore, the abnormal electrocardiographic response to standard exercise correlated well with the history that the patient was ill and incapacitated. This case also revealed that double the amount of exertion produces more marked electrocardiographic changes than the standard two-step test.

Group 3, Angina Pectoris and Abnormal Electrocardiogram.—Of the 26 patients with angina pectoris whose control electrocardiograms were abnormal, changes were observed in 50 per cent after the standard number of climbs and in two-thirds after double the standard number of trips (Table III). The test in this group was therefore positive more frequently than among the patients of Group 2, who had normal control electrocardiograms.

CASE 3.—Fig. 5 shows the electrocardiograms of a man (M. P.), 62 years of age, who was suffering from angina pectoris caused by coronary disease. The pain often occurred at rest, as well as on effort, and was sufficiently severe to prevent work. A mild, transient hypertension, slight left ventricular enlargement, and distant heart sounds were the important points in the clinical examination. The electrocardiogram was somewhat abnormal, i.e., QRS measured 0.10 to 0.11 second, T_2 was small, and T_3 was inverted. Significant transient abnormalities appeared after exercise. After the double two-step test, i.e., 34 ascents in three minutes, the RS-T segment in Leads I and II became depressed at least 1 mm. below the isoelectric level, and T_4 became smaller. Three minutes after the exercise, T_4 was flat. Here again the abnormality in the electrocardiogram after the exercise correlates well with the known clinical facts, i.e., severe subjective symptoms with an only slightly abnormal control electrocardiogram.

Groups 4 and 5, Previous Coronary Occlusion.—The 53 patients who had had acute coronary artery occlusion previously were also divided into two groups: 10 whose electrocardiograms after the attack had become normal, and 43 whose tracings remained abnormal. In the first group, whose cardiac function was better, there were no positive results with the standard two-step test, and only one patient gave an abnormal response after the double exertion (Table III). Of the second, larger group with abnormal electrocardiograms, almost one-half showed a positive response to the standard and double two-step exercise. Thus, in this group, also, the electrocardiogram after exercise correlates with the pa-

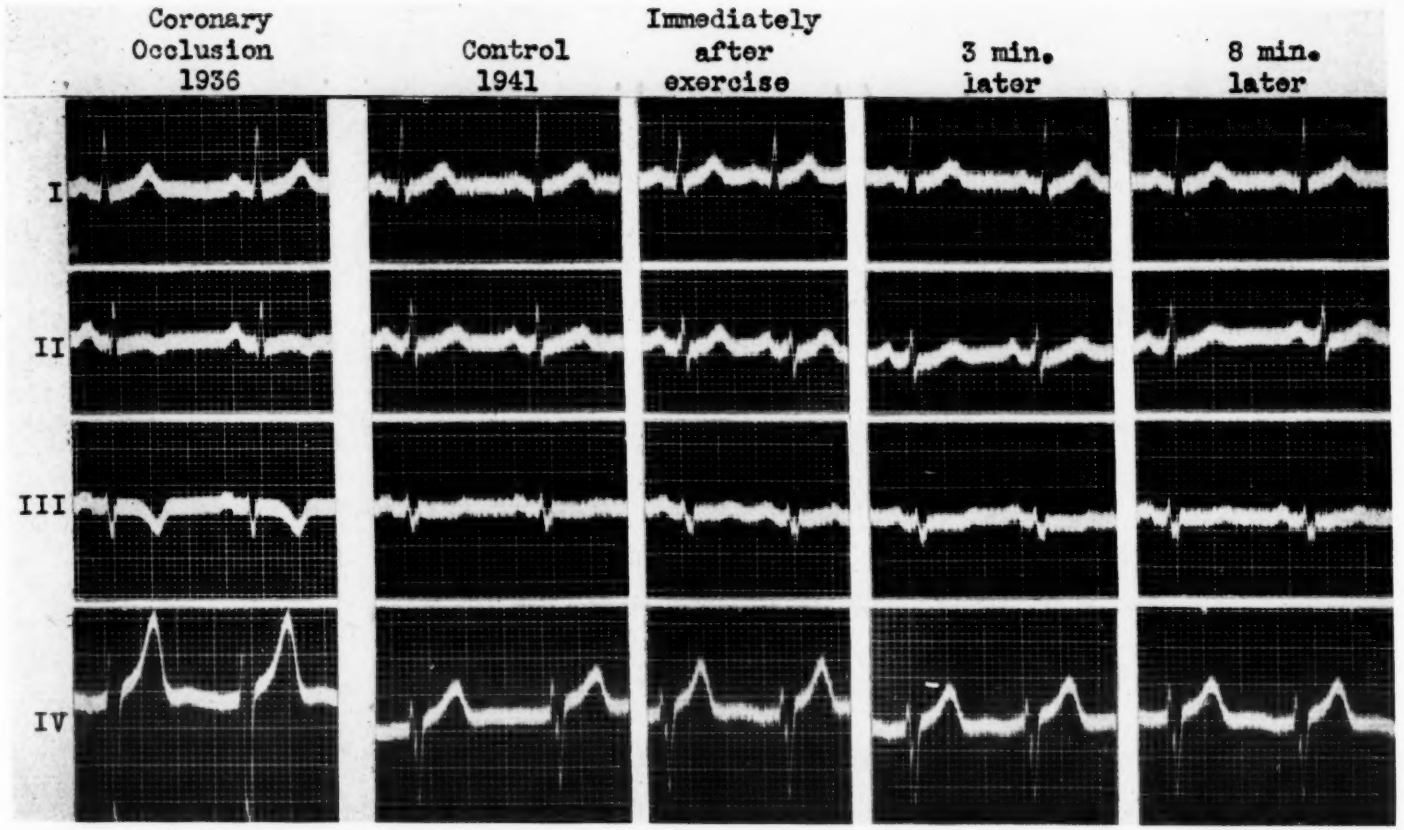

Fig. 6.—Case 4 (F. C.), a man 40 years of age, who had acute coronary occlusion five years earlier and made a complete recovery. Electrocardiogram in 1936 shows inverted T_2 and T_3. Control record in 1941 is normal. No changes occurred after the double standard two-step test (42 trips in 3 minutes).

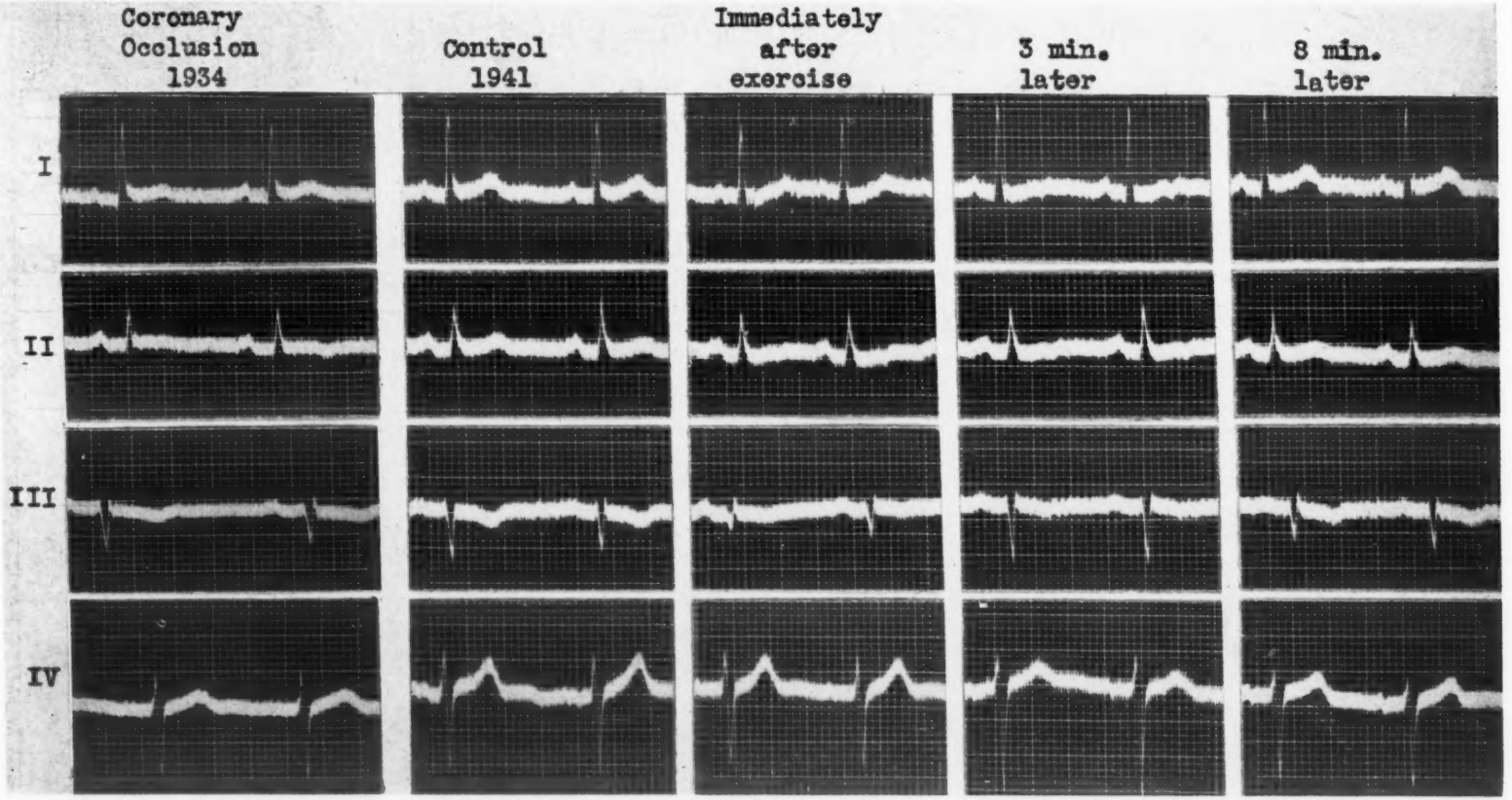

Fig. 7.—Case 5 (P. G.), a man of 60 who had acute coronary occlusion 7 years before; since then he has had moderately severe angina pectoris. Electrocardiogram in 1934 shows semi-inverted T_2 and T_3. Control record in 1941 is normal except for T_3 inversion. After the double standard two-step test (38 trips in 3 minutes) $S\text{-}T_1$ and $S\text{-}T_2$ are slightly depressed, and T_1 and T_2 semi-inverted.

tient's cardiac function; the changes are more pronounced when function is known to be poor. In the following cases the electrocardiogram returned to normal after coronary occlusion.

CASE 4.—In the first case, that of a man of 40 (F. C., Fig. 6), even a double two-step test produced no significant changes in the electrocardiogram. This was not unexpected, for, although the patient had had acute myocardial infarction in 1936 (five years earlier), he had made a complete recovery; he was entirely asymptomatic and the cardiac function was normal as judged clinically and by laboratory study. He was working full time at his old occupation as a salesman without any difficulty at all. The size of the heart, heart sounds, electrocardiogram, cardiac pulsations, and exercise tolerance test were entirely normal. No evidence of coronary insufficiency could be elicited, even by the double two-step test.

CASE 5.—Fig. 7 shows the result of the test on a 53-year-old man (P. G.) who had had acute coronary occlusion seven years before. He was a large, hyposensitive man, a doorman who could not work because of pain on effort. Although the electrocardiogram had returned to normal, other clinical signs of coronary insufficiency persisted. The exercise tolerance test (blood pressure and pulse rate reactions) was below average, and pain in the chest occurred during the test. Clinically he was considered an ill man, in spite of the normal electrocardiogram. After the double two-step exercise, the electrocardiogram became definitely abnormal; semi-inversion of T_1 and T_2 appeared. This case also demonstrates the correlation of the test with the patient's history.

CORRELATION OF ELECTROCARDIOGRAM WITH BLOOD PRESSURE AND PULSE RATE AFTER EXERCISE

The cases reported above have given evidence that the character of the electrocardiogram after standard exercise is a good measure of cardiac function. Further evidence is obtained by comparing the results of this test with those of the ordinary exercise tolerance test. These are presented in Table IV. The exercise tolerance in the normal control group and in the cases of angina pectoris was ascertained by the blood pressure and pulse rate reaction to the standard two-step exertion. Repeated blood pressure and pulse rate readings were recorded until basal levels were attained.[2] Then the patient made the number of trips required for his age and weight in exactly a minute and a half. Within two

TABLE IV

CORRELATION OF CARDIAC FUNCTION, AS ASCERTAINED BY BLOOD PRESSURE AND PULSE RATE RESPONSE TO TWO-STEP TEST, WITH ELECTROCARDIOGRAPHIC RESPONSE TO STANDARD EXERCISE

Group	Cardiac Function	STANDARD TWO-STEP TEST		DOUBLE STANDARD TWO-STEP TEST	
		No. of Cases	% Positive	No. of Cases	% Positive
1. Normal adults	Good	65	0	30	0
	Poor	0	0	0	0
2. Anginal pectoris with normal control E.C.G.	Good	25	12	18	22
	Poor	27	19	18	44
3. Angina pectoris with abnormal control E.C.G.	Good	4	25	3	33
	Poor	21	62	10	90

minutes after cessation of the exercise, the blood pressure and pulse rate should return to within ten points of the resting (basal) figures. Otherwise, the exercise tolerance was considered poor or below average.[2] It is necessary to have the patient always turn toward the examiner at the beginning of a reascent. (This meant always turning in a different direction, so that dizziness and the resulting changes in blood pressure were prevented.)

In the healthy controls (Group 1), the exercise tolerance was uniformly good and the electrocardiograms always remained normal (Table IV). In the angina pectoris group with normal control electrocardiograms (Group 2), there was a distinctly larger percentage of abnormal electrocardiographic responses among those with poor exercise tolerance, as compared to those with a normal tolerance; the respective percentages were 12 per cent, compared with 19 per cent, and 22 per cent, compared with 44 per cent, depending on whether the standard or doubled two-step exercise was utilized (Table IV). In the group of patients who had angina pectoris and abnormal control electrocardiograms (Group 3), the percentage of abnormal electrocardiographic responses after the two-step exercise was again larger among those with poor cardiac function than among those with normal cardiac function, as measured by the blood pressure and pulse rate response. After the standard two-step exercise the incidence of abnormal electrocardiographic changes in those with normal cardiac function was 25 per cent, and, in those with poor cardiac function, it was 33 per cent. Similarly, after the double two-step exertion, the percentages were 62 and 90, respectively (Table IV).

CHARACTER OF ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

Table V summarizes the changes in the four leads of the electrocardiograms of patients with the anginal syndrome. Similar abnormalities were observed in the other groups of patients. RS-T depression of more than ½ mm. below the isoelectric level in any lead was the most frequent abnormality encountered. It was found most commonly in Leads I and II. This applied also to T-wave changes, which were less frequent than RS-T depression. In other words, the limb leads were abnormal oftener than the chest lead, but all leads were helpful. Occasionally the precordial lead showed abnormalities when there were none in the standard limb leads.

TABLE V

INCIDENCE OF ELECTROCARDIOGRAPHIC CHANGES (RS-T AND T WAVE) IN DIFFERENT LEADS AFTER EXERCISE IN PATIENTS WITH ANGINA PECTORIS

	Lead I	Lead II	Lead III	Lead IV
1. Angina pectoris with normal control electrocardiogram	19	22	4	12
2. Angina pectoris wiah abnormal control electrocardiogram	21	21	1	8

DISCUSSION

A great deal has been written on the subject of the electrocardiogram after exercise, and a review of the literature will be found in the papers of Feil[5] and Riseman, Waller, and Brown,[10] which should be consulted. It is essential that a standard amount of exercise be performed, for many authors[5-10] have shown that excessive work may produce significant electrocardiographic changes in normal persons. That is why we used the standard or double two-step tests, which produce no significant electrocardiographic changes in normal persons. When definite alterations appear in the electrocardiogram after the two-step exercise test, the patient is not normal. In our experience the test has proved to be of practical value. At times, the electrocardiogram after standard two-step exercise may be abnormal when physical and laboratory examination is entirely negative (Case 1). It is to be remembered, however, that the test is significant only when it is positive, that is, when electrocardiographic changes occur after standard exercise. Not every patient who has organic heart disease, whether it be coronary sclerosis, syphilitic aortitis, or aortic insufficiency, gives a positive response. Therefore, the absence of electrocardiographic changes after standard exercise does not rule out the presence of organic heart disease.

The electrocardiographic changes which occur after exercise, namely, depression of the RS-T segment and lowering or inversion of the T wave, are similar to those which occur with a spontaneous attack of angina pectoris[5, 10] or in acute coronary insufficiency[11, 12] caused by hemorrhage, shock, heart failure, or tachycardia. They are more transient than the changes observed in the latter conditions. They are due to the anoxemia of the myocardium which results from a discrepancy between the coronary blood flow and the increased demand of the myocardium for oxygen. In other words, the exercise induces a transient coronary insufficiency which is relieved in a few minutes by rest. The electrocardiographic changes are also similar to those caused by generalized anoxemia.[13-15]

We have never observed any significant elevation of the RS-T segment after exercise, although occasional instances have been reported by several authors.[6, 16, 20] It must be extremely uncommon, however. The changes after exercise are not like those of acute coronary artery occlusion, for no Q waves appear, and, with the exception of the above quoted isolated cases, elevation of RS-T and a reciprocal relation between Leads I and III do not occur. As already stated, the changes which do appear are typical of acute coronary insufficiency, but not of coronary occlusion.

The two-step test is a simple, quantitative one. It is without danger, and utilizes exercise to which everyone is accustomed, no matter how sedentary his work is. We have never seen pain develop in normal subjects, and this has also been the experience of Feil.[5] If pain develops in

a case of coronary artery disease, the test can be continued, provided the pain is not severe. Even the presence of pain may not affect the results.

It is possible to perform the two functional tests of the heart at once, that is, one can record the electrocardiogram as well as the blood pressure and pulse rate after the standard exercise. The combined test should preferably be performed by two persons; one records the electrocardiograms and the other obtains the blood pressure and pulse rate readings, but, with training, one person can record the electrocardiogram within one minute and the blood pressure and pulse rate during the next minute. The two tests are better than one in evaluating cardiac function or as aids in making a diagnosis. Prognosis, too, should not be judged by one test alone, but by utilizing all possible observations.

The changes in the electrocardiogram usually last only a few minutes, rarely more than eight to fifteen minutes. Occasionally they disappear within one minute after cessation of the exercise. This emphasizes the importance of recording the first electrocardiogram as quickly as possible after the exercise. The electrodes are therefore kept strapped to the patient's arms and leg while he climbs the steps, so that the electrocardiogram can be taken the moment the climbs are finished (Fig. 1).

The P-R segment was chosen as the isoelectric level only after considerable experimentation. In electrocardiograms in which the heart rate was rapid, it was found that the P-R segment was the only portion of the curve in which the level remained unchanged. Naturally, after exercise, the heart beat is accelerated and diastole (represented by the T-P interval) is shortened. The T-P segment remains elevated because there is insufficient time for it to reach its true isoelectric level before the next beat. The RS-T segment will then show an apparent depression below the T-P segment. Furthermore, a U wave often appears after exertion, or may have already been present, and this, also, elevates the T-P segment above its correct isoelectric level. If one carefully examines the electrocardiogram when the heart rate is slow, it will be seen that the T-P segment nearly always slants downward slightly and reaches its lowest level after a long diastole. The lowest level is always the same as the P-R level. When the heart rate is increased, the T-P segment is shortened and fails to reach the true isoelectric line. Riseman, Waller, and Brown[10] also used the P-R level as the isoelectric level with which to compare the changes in the RS-T segment after exercise. A depression of the RS-T segment of only 0.5 mm. would at first appear to be insignificant and insufficient as a criterion of abnormal response to exercise. However, we have found that if the P-R segment is used as a control, a depression of more than 0.5 mm. never occurs in normal persons.

We have described two variations of the test for electrocardiographic changes after exercise, namely, one based on the standard amount, and the other on double that amount, of two-step exercise. The former, which is less strenuous and is completed in one and one-half minutes,

should be used for patients who are known to have, or suspected of having, some impairment of the heart. It is thus indicated for those with the anginal syndrome and those who have had previous attacks of coronary occlusion, coronary insufficiency, or paroxysmal dyspnea, and in the presence of valvular, syphilitic, or congenital heart disease. It should prove of value also in annual physical examinations and examinations for retirement. The electrocardiogram after double the standard two-step exercise, i.e., exertion for three minutes at a standard rate, may be used for testing military recruits, young and middle-aged persons, or any patient in the previously mentioned groups whose electrocardiogram after standard two-step exertion has remained normal. Anyone with a normal or practically normal electrocardiogram should have this double exertion test. In hundreds of tests with the double two-step exercise we have never seen any harmful or really painful result. Of course, this somewhat more strenuous exercise test should not be used on a patient who is acutely ill or when an acute illness is just subsiding. As a general rule, subjects 50 years of age or older should be subjected to the standard test first.

SUMMARY AND CONCLUSIONS

1. A new modification of a test of heart function is described; it utilizes the effect of a definite amount of work on the electrocardiogram. The work consists of the two-step exercise tolerance test, employing the standard number of climbs or double that number. By this method the exertion is limited to a definite amount, and is standardized for the patient's age, sex, and weight.

2. No significant electrocardiographic changes after these tests have been observed in normal persons. Depression of the RS-T segment more than 0.5 mm. below the P-R segment or flattening or inversion of the T wave is abnormal, and is indicative of coronary insufficiency.

3. Changes were observed after the standard test in one-fifth of the cases of angina pectoris with normal control electrocardiograms, and in two-fifths after the double test; of the cases in which the control electrocardiogram was abnormal, they occurred in one-half after the standard test and in two-thirds after the double test.

4. The RS-T and T-wave changes occurred most commonly in Leads I and II and disappeared within eight minutes. They were similar to those caused by anoxemia and acute coronary insufficiency.

5. The test is particularly useful in studying patients with symptoms of heart disease when other methods of examination, including the electrocardiogram, are negative. A negative test does not exclude the presence of organic heart disease.

6. Correlation of the results of the test with the patient's clinical status, as ascertained from symptoms, cardiac examination, and the exercise tolerance test, has shown that the test is a good measure of cardiac function.

7. The test is simple to perform, is not dangerous except for very ill patients, and is useful in diagnosis, prognosis, and in following the patient's progress. It can be combined with the exercise tolerance test; i.e., the pulse rate and blood pressure, as well as the electrocardiogram, can be recorded after the standard exercise. The electrocardiographic, pulse rate, and blood pressure responses to standard and double exercise are useful as cardiac fitness tests in military and aviation medicine.

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HYPOPLASIA OF THE AORTA WITHOUT TRANSPOSITION WITH ELECTROCARDIOGRAPHIC AND HISTOPATHOLOGIC STUDIES OF THE CONDUCTION SYSTEM

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THERE are a number of anomalies of the heart which include hypoplasia of the aorta. These may be classified as follows:

(1) Hypoplasia of the aorta associated with transposition;
(2) Hypoplasia of the aorta not associated with transposition,
  (a) with aortic and/or mitral stenosis or atresia,
  (b) without mitral or aortic stenosis or atresia.

In a series of fifty congenitally malformed hearts studied by one of us (M. L.) at the Michael Reese Hospital, hypoplasia of the aorta was present in 20 per cent. However, it was associated with mitral or aortic atresia in only three cases. The subject has been dealt with recently by Evans,[1] Roberts,[2] McNerney,[3] Abbott,[4] Monserrat,[5] Rukstinat,[6] Lippincott,[7] von Haam and Hartwell,[8] Baggenstoss,[9] and Anderson and Sano.[10]

Electrocardiographic studies of congenital aortic atresia and stenosis have been reported in only one instance.[10] Histologic studies of the conduction system in congenitally malformed hearts are few.[11] The present report deals with both studies in two cases.

CASE 1.—

History.—This male child was born July 30, 1940; it was a normal delivery. The duration of gestation was 8 months. The birth weight was 2460 grams, and the child measured 46 cm. in length. At birth the infant was moderately cyanotic, and the cyanosis increased during the first day as its condition became worse. The respirations were rapid and shallow. Bronchial breathing and râles were heard at the bases of both lungs. There was a short systolic murmur over the precordial area, and the pulmonic second sound was accentuated. The liver was palpable two fingerbreadths below the right costal margin. On the second day of life the cyanosis became more marked, the abdomen became distended, vomiting occurred, and there was twitching of the left side of the face and left arm and leg. Treatment consisted of oxygen, gastric lavage, vitamin K intramuscularly, fluids subcutaneously, and stimulants. These were of no avail, however, and the child died forty-four hours after birth.

A roentgenogram of the chest (Fig. 1) was read as follows: "The superior mediastinum is widened, with the lateral walls almost vertical. The findings suggest an enlarged thymus. The heart shadow is large and globular, with the bulk of the heart to the left of the midline. This finding would suggest the possibility of a congenital heart. The lung field markings in the right lower, and the left mid-lung field, are exaggerated."

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An electrocardiogram (Fig. 2) revealed the following: "Rate is 107. P-R interval is 0.16 second. QRS_1 is M-shaped, mainly inverted, and tiny. QRS_2 and QRS_3 are upright, slurred, and small. QRS duration is 0.14 second. T_1 and T_2

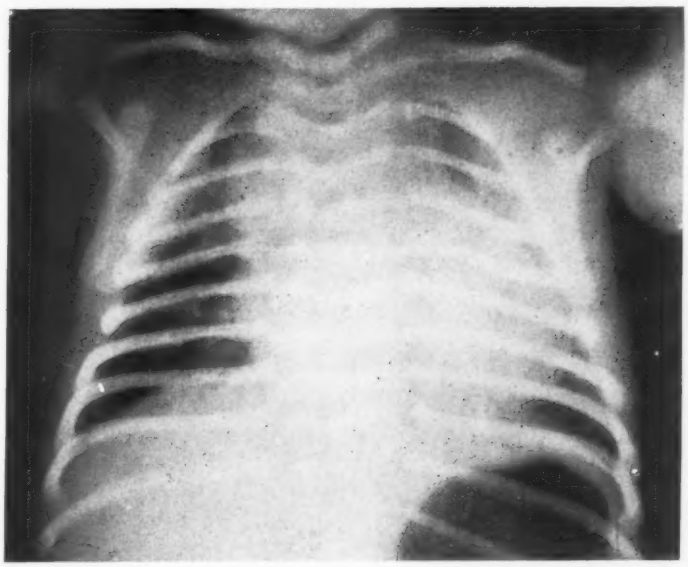

Fig. 1.—Roentgenogram of chest in Case 1. Note the large and globular shaped heart, especially prominent in the left side of the chest. Described in text.

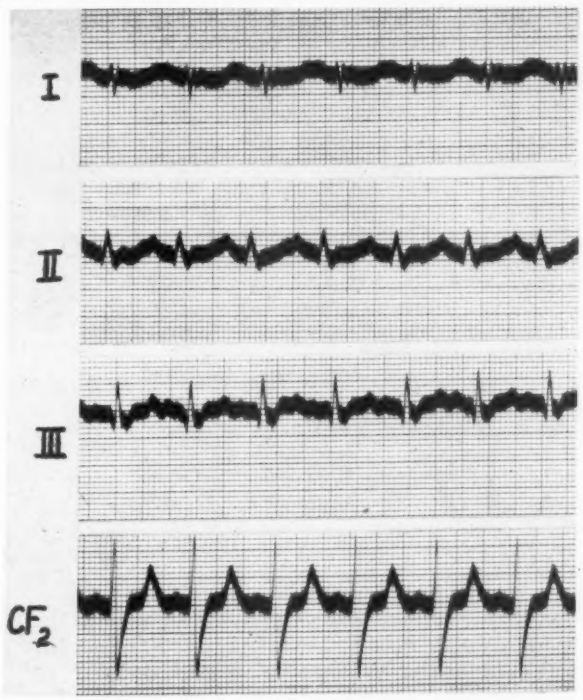

Fig. 2.—Electrocardiogram in Case 1. Described in text.

are small. Lead CF_2 is normal in configuration but there is prolongation of the P-R interval and the QRS duration. Interpretation: Sinus rhythm. First degree auriculo-ventricular block. Intraventricular block of the indeterminate type with low 'voltage.' Definitely abnormal curve.''

Clinical Diagnosis.—Congenital heart disease, with circulatory insufficiency. Extensive, fulminating bronchopneumonia. Pulmonary atelectasis. Possibly cerebral hemorrhage.

Post-Mortem Examination.—Aside from the abnormalities in the heart, the pathologic diagnoses were: (1) prematurity; (2) subarachnoid hemorrhage; (3) pin-point intracerebral hemorrhages; (4) hemorrhages into both kidneys; (5) partial pulmonary atelectasis; (6) hyperemia of all the organs.

Heart.—(Figs. 3 and 4). The heart was triangular in shape. The apex was formed by the right ventricle. From the base of the heart two vessels emerged: a large one situated to the left and somewhat anteriorly, and a small one situated to the right and somewhat posteriorly. The mutual relationships of the various heart chambers were normal.

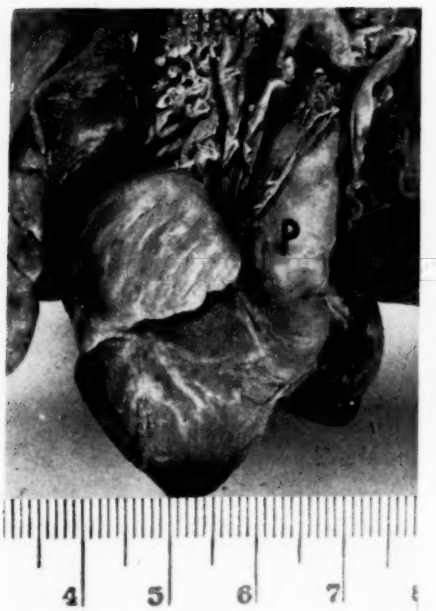

Fig. 3.

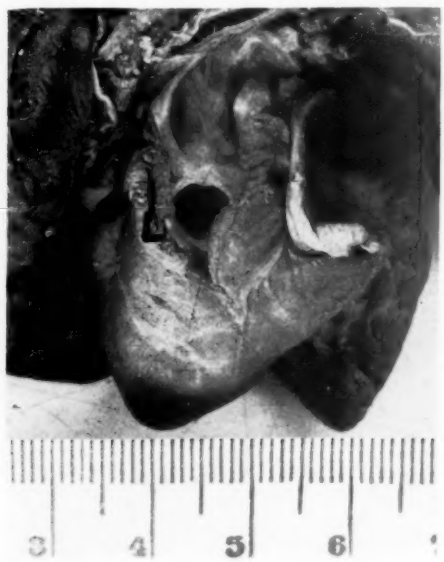

Fig. 4.

Fig. 3.—Anterior view of the heart in Case 1. Note the hypoplastic aorta and large pulmonary artery; A, aorta; P, pulmonary artery.

Fig. 4.—Left auricular and ventricular view of the heart in Case 1. Note the hypoplastic left ventricle; L, left ventricle.

The right auricle was markedly dilated and its wall was relatively thickened; the latter measured as much as 1 mm. in thickness. The superior and inferior venae cavae and coronary sinus entered this chamber normally. The Eustachian and Thebesian valves formed one curtain guarding the inferior vena cava and the coronary sinus. The limbus in its upper portion was well formed but was deficient in its anteroinferior portion. The septum primum was well formed. There was no anatomic unity between the septum primum and the limbus; this produced a directly patent foramen ovale, the diameter of which was 5 mm.

The tricuspid orifice measured 4.3 cm. in circumference. The tricuspid valve and its chordae tendineae and papillary muscles were normal.

The right ventricle was markedly enlarged; the thickness of its wall was 1 mm. at the pulmonic orifice, 2 mm. at the tricuspid orifice, and 1 mm. at the left lateral margin. The muscle bundles of the right ventricle were normal in contour. From this chamber emerged the pulmonary artery. This was the large vessel which had been seen externally, to the left and anteriorly.

The pulmonic orifice measured 2.6 cm. in circumference. It was guarded by a normal right cusp and a large cusp situated to the left and anteriorly. The latter cusp was incompletely divided into two parts, a left and anterior portion, by a low band traversing the region of the sinus of Valsalva. The pulmonary artery gave off the right and left branches normally. The ductus arteriosus was widely patent. The muscular interventricular septum was complete. The "pars membranacea," however, was muscular.

The left auricle was relatively small, and its wall was relatively thin. It received the four pulmonary veins normally. The mitral orifice measured 1.3 cm. in circumference. The left auriculoventricular valve consisted of a semilunar band of endocardial tissue which was attached to two greyish-white ridges in the anterior and posterior walls of the left ventricle. These ridges were in the normal position of the anterior and posterior papillary muscles of the left ventricle in the normal heart.

The left ventricle was a minute chamber, and its wall measured as much as 3 mm. in thickness. Its lining was greyish-white, opaque, and thickened. In the region where the normal aorta should have emerged, there was a slight puckering. However, no vessel was seen to emerge from the left ventricle.

The small vessel which emerged externally to the right and posteriorly was the aorta; however, it did not enter the heart. The proximal portion of the aorta ended in an irregularly puckered area at the base of the heart without valvular structure. In this region the right and left coronary arteries emerged. The course and distribution of the coronary arteries were normal. The circumference of the ascending aorta measured 5 mm. The transverse portion of the aorta gave off the brachiocephalic vessels normally. Its circumference measured 8 mm. The transverse aorta united with the ductus arteriosus to form the descending aorta, which measured 8 mm. in circumference.

Histologic studies of the myocardium revealed a marked increase in connective tissue in the myocardium adjacent to the endocardium. The perivascular connective tissue was especially increased about many arteries, the lumens of some of which were narrowed. Also, the endocardium presented a marked increase in connective tissue. This was partially hyalinized and contained small foci of calcium deposits. Both the mitral and tricuspid valves showed an increase in connective tissue. There was no distinct evidence of active inflammation anywhere in the heart.

The Purkinje system was studied by incomplete serial sections stained with hematoxylin and eosin and by the van Gieson method. The auriculoventricular node, the bundle of His, and the left branch were clearly recognizable anatomically. The right branch could not be identified. The auriculoventricular node revealed no pathologic change (Fig. 8). The bundle of His, however, was embedded in a large mass of scar tissue (Fig. 9). Masses of this tissue invaded the bundle, and there was a distinct disruption in continuity of some of its fibers and in the fibers of the beginning of the left branch. In addition, the distal portion of the left branch lay encased in, and was irregularly subdivided by, the markedly increased hyalinized connective tissue in the endocardium of the left ventricle (Fig. 10).

CASE 2.—

History.—This male infant was born June 25, 1937, after a normal full-term pregnancy; the delivery was normal. It weighed 4,215 grams and measured 50 cm.

in length. The mother, aged 22 years, had one other child who was living and well. After birth the child was cyanotic; it died June 27, after having lived forty-five hours.

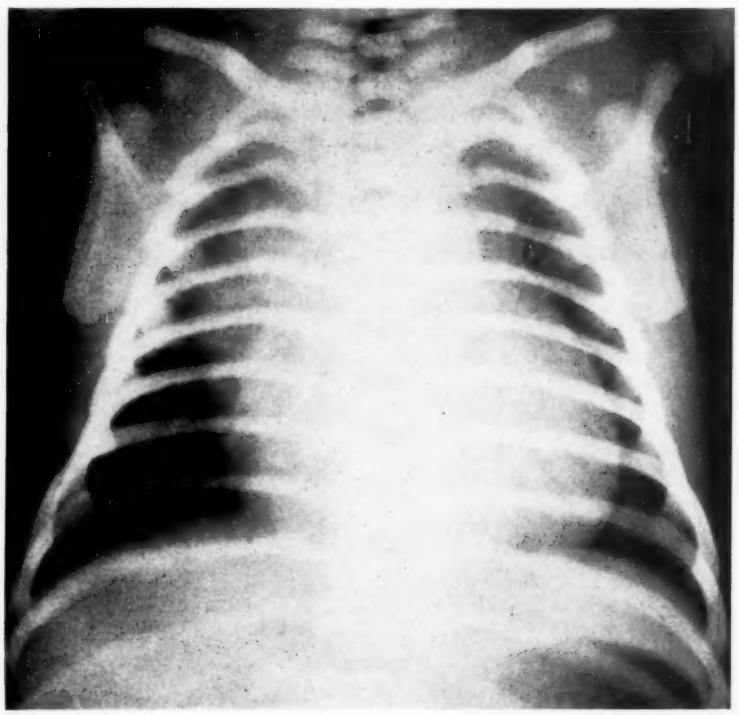

Fig. 5.—Roentgenogram of chest in Case 2. The heart is enlarged. Described in text.

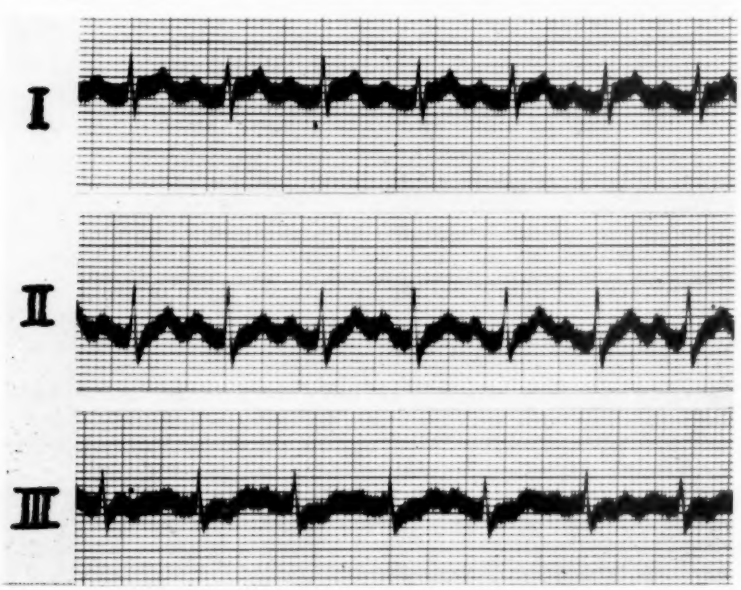

Fig. 6.—Electrocardiogram in Case 2. Described in text.

A roentgenogram of the chest (Fig. 5) showed that the heart outline was larger than normal and rather globular. A haziness involved almost the entire right upper lobe and a portion of the left upper lobe, suggesting atelectasis. No thymus was recognized.

An electrocardiogram (Fig. 6), taken June 27, revealed the following: "Rate is 125. P-R interval is 0.20 second. QRS is up in all leads and small. QRS duration is 0.08 second. S-T_1 and S-T_2 are elevated, and S-T_3 depressed. T_3 is small. Interpretation: Sinus rhythm. First degree auriculoventricular block. Intraventricular block of the indeterminate type with low 'voltage.' Definitely abnormal curve."

Post-Mortem Examination.—Aside from the heart, the pathologic diagnoses were: (1) confluent bronchopneumonia; (2) hemorrhages in the lung, thymus, peripancreatic tissue, and mesentery.

Heart.—(Fig. 7). The heart was somewhat enlarged and globular in shape. The apex was formed by the right ventricle. From the base, two vessels were seen to emerge, a larger one anterior and to the left, and a smaller one, posterior and to the right. The mutual relationships of the various heart chambers were normal.

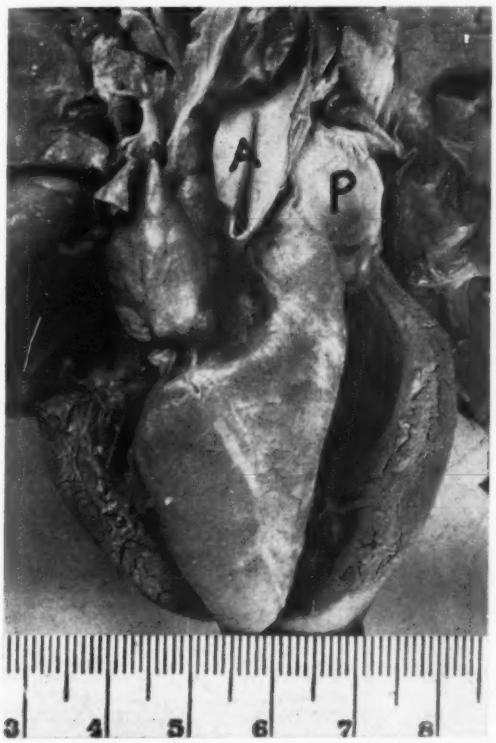

Fig. 7.—Anterior view of the heart in Case 2. Note the hypoplasia of the aorta, the dilatation of the pulmonary artery, and the right ventricular hypertrophy; A, aorta; P, pulmonary artery.

The right auricle was enlarged, and its wall was somewhat thickened. The superior and inferior venae cavae and coronary sinus entered this chamber normally. The Eustachian and Thebesian valves were absent. The limbus (septum secundum) was well formed in its upper portion, but deficient in its lower. It described an incomplete arc, measuring 0.8 cm. in greatest diameter. The septum primum was well formed, and its free edge pointed anterosuperiorly. The septum primum and

secundum were not anatomically united, leaving an obliquely shaped, widely patent foramen ovale which measured 0.6 cm. in greatest diameter.

The right auriculoventricular orifice measured 4.5 cm. in circumference. It was guarded by a valve consisting of two large leaflets, an anterior and a septal. The anterior leaflet had the topography of the normal anterior leaflet of the tricuspid valve, and was connected to a normally formed but thickened anterolateral papillary muscle. The septal leaflet presented numerous chordae tendineae, attached

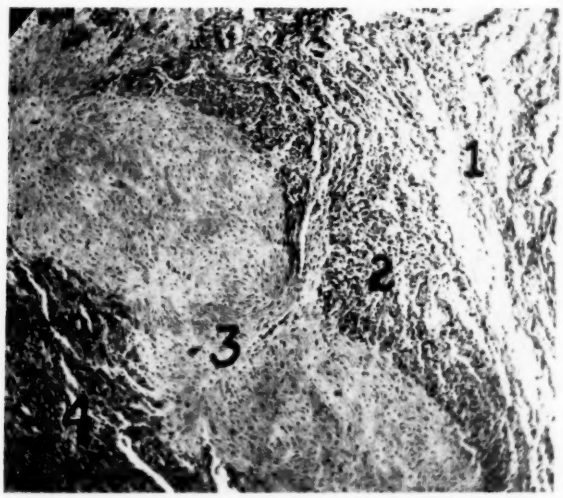

Fig. 8.—The A-V node in the region of the central fibrous body in Case 1. Hematoxylin-eosin preparation, ×52. There is no abnormality; 1, auricular musculature; 2, A-V node; 3, central fibrous body; 4, ventricular musculature.

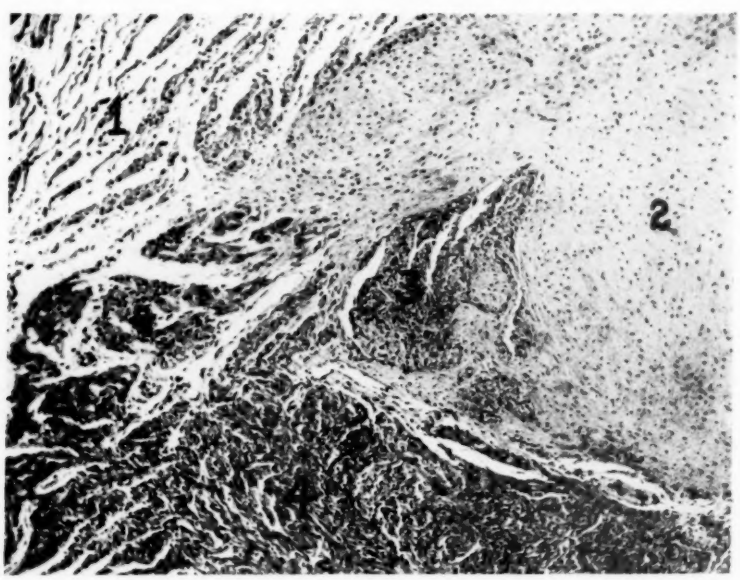

Fig. 9.—The bundle of His in Case 1. Hematoxylin-eosin preparation, ×72. Note the disruption of the bundle as it gives off the left bundle branch; 1, auricular musculature; 2, fibrous tissue at the base of the atretic aorta; 3, bundle of His; 4, beginning of left branch.

directly to the trabeculae carneae of the right ventricle. There was no posterior papillary muscle in the right ventricle.

The right ventricle was markedly enlarged and occupied most of the heart. Its wall measured 2 mm. at the left lateral margin. The septal and parietal muscle bundles were normally formed, but thickened, especially the latter. The vessel

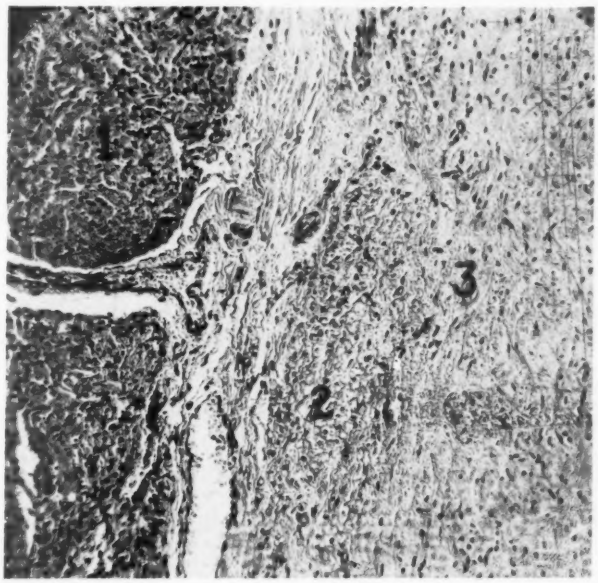

Fig. 10.—Portion of the left bundle branch in Case 1. Hematoxylin-eosin preparation, ×120. There are marked degenerative changes in the muscle fibers of the bundle branch as it lies in the markedly thickened and fibrous endocardium. Connective tissue interrupts the continuity of the muscle fibers; 1, ventricular musculature; 2, bundle branch fibers; 3, markedly thickened endocardium.

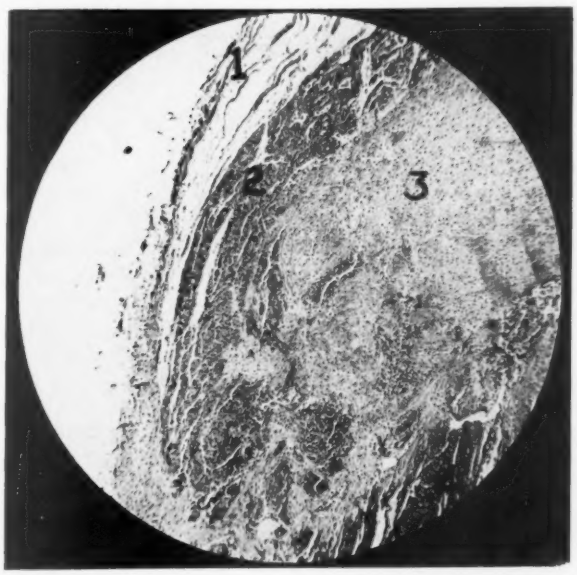

Fig. 11.—The A-V node in Case 2. Hematoxylin-eosin preparation, ×40. There is no abnormality; 1, auricular musculature; 2, the A-V node; 3, central fibrous body; 4, ventricular musculature.

emanating from this chamber was the pulmonary artery. This was the large vessel situated anteriorly and to the left. Its orifice measured 2 cm. in circumference. Its valve consisted of three cusps which were in normal position. The artery gave off the right and left pulmonary branches normally. The ductus arteriosus was widely patent.

The left auricle was small in comparison to the right. It received the four pulmonary veins normally. The left auriculoventricular orifice was correspondingly small and measured 2 cm. in circumference. Its valve leaflets, chordae tendineae, and papillary muscles had the topography of the normal mitral valve.

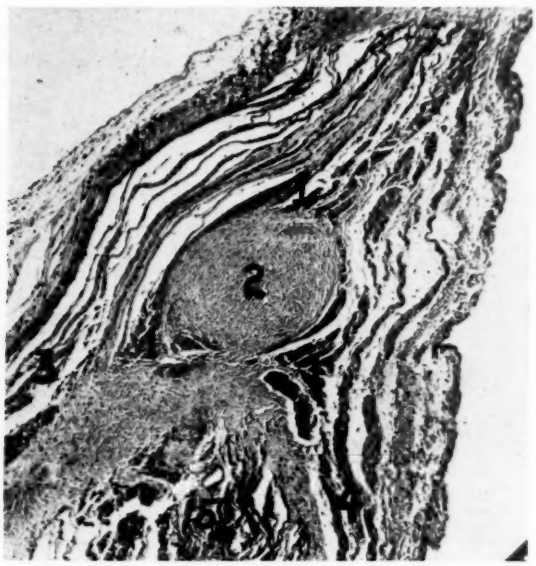

Fig. 12.—The bundle of His, with its branching, in Case 2. Hematoxylin-eosin preparation, ×56. Note the large mass of connective tissue displacing the muscle fibers of the main bundle; 1, bundle of His; 2, fibrous tissue in the bundle; 3, right bundle branch; 4, left bundle branch; 5, ventricular musculature.

The left ventricle was so small that it appeared almost as an appendage of the right ventricle. Its wall measured 3 mm. in thickness. The muscular interventricular septum was topographically normal. The pars membranacea was replaced by muscle. Emanating from this chamber was the aorta. This was the small vessel which had been noted externally, posterior and to the right of the pulmonary artery. The orifice of this vessel was small, measuring 1 cm. in circumference. The aortic valve consisted of three normally formed, but minute, cusps. The coronary ostia and distribution of the coronary arteries were normal. The circumference of the ascending aorta measured 1.1 cm. The brachiocephalic vessels were given off normally. The circumference of the transverse aorta measured 1 cm., whereas that of the descending aorta measured 1.2 cm.

Histologic study of the myocardium revealed a moderate increase in connective tissue in the right ventricular septal myocardium adjacent to the endocardium. The vessels showed no changes. The fibers of the myocardium of the right ventricle were distinctly larger than those of the left ventricle. The mitral and tricuspid valves showed no changes.

The Purkinje system was studied by incomplete serial sections, stained with hematoxylin and eosin and by the van Gieson method. The auriculoventricular node and the bundle of His and its two arborizations were clearly recognizable anatomically. There was no pathologic change in the auriculoventricular node

(Fig. 11). However, in the center of the bundle of His there was an oval mass of connective tissue which displaced the medial fibers of the bundle and sent fibrous cords among the muscle fibers themselves (Fig. 12). Both the right and left bundle branches showed focal degeneration of the fibers and interruptions by connective tissue (Figs. 13 and 14).

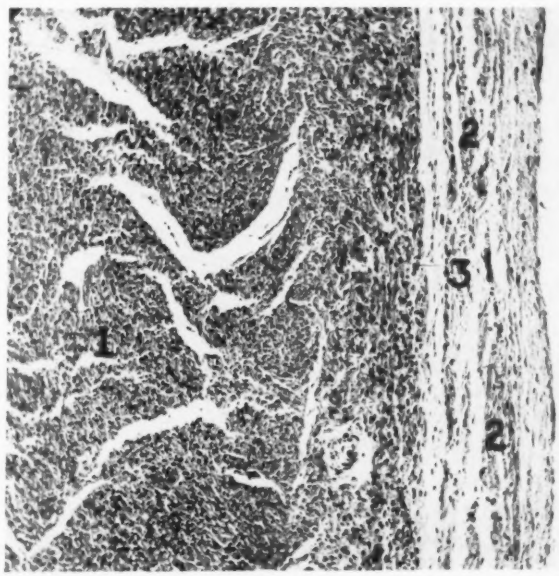

Fig. 13.—Left bundle branch in Case 2. Hematoxylin-eosin preparation, ×72. Connective tissue in the endocardium interrupts the continuity of the muscle fibers; 1, ventricular musculature; 2, bundle branch; 3, connective tissue interruption.

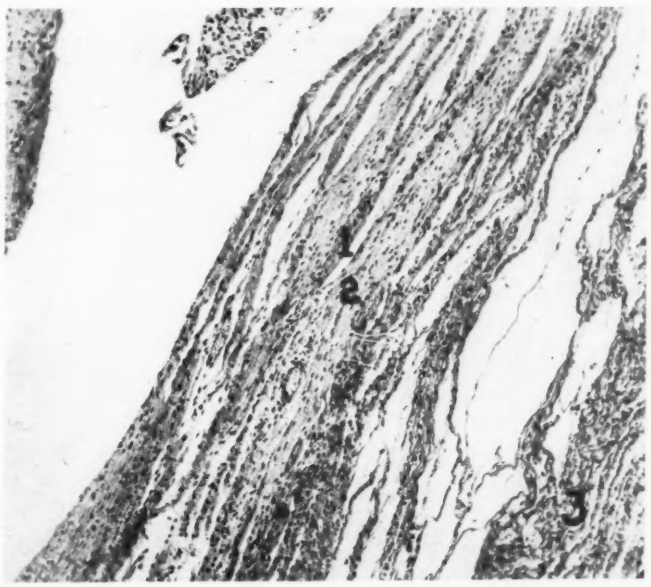

Fig. 14.—Right bundle branch in Case 2. Hematoxylin-eosin preparation, ×64. Note the marked replacement of the muscle fibers of the bundle by endocardial connective tissue; 1, bundle branch fibers; 2, connective tissue; 3, ventricular musculature.

ANATOMIC AND EMBRYOLOGIC DISCUSSION

The anatomic features common to both hearts were: (1) hypoplasia of the ascending and transverse portions of the aorta; (2) hypoplasia of the left auricle, ventricle, and mitral orifice; (3) patent ductus arteriosus and foramen ovale; (4) complete ventricular septum; (5) marked hypertrophy and dilatation of the right auricle and ventricle; (6) no transposition; and (7) abnormal Eustachian and Thebesian valves. In addition, there were, in the first case, (1) atresia of the aortic orifice; (2) marked fibrous thickening of the endocardium of the left ventricle; (3) diffuse equal thickening of the mitral leaflets; and (4) an incompletely divided tricuspid pulmonic valve, and in the second case, (1) hypoplasia of the aortic orifice, and (2) bicuspid "tricuspid" valve.

Case 1 thus belongs to type 2 (a) of our classification, and Case 2 belongs to type 2 (b). In type 2 there is no transposition of the arterial trunks, a defect of the auricular septum is always present, and there may be a defect of the ventricular septum. The ductus arteriosus is usually patent, and there are hypertrophy of the right ventricle and a varying degree of hypoplasia of the left ventricle. When there is aortic atresia or stenosis, with or without mitral atresia or stenosis, the left ventricle is minute or absent, and its endocardial lining usually presents marked fibrous thickening. There may be various minor associated lesions, such as an abnormality of the valves, including the Eustachian and Thebesian valves.

In type 1, hypoplasia of the aorta is associated with various types of transposition of the arterial trunks. Although it is usually the pulmonary trunk which is inhibited in transposition (tetralogy of Fallot), occasionally the reverse may be true (tetralogy of Eisenmenger[12]).

There are various degrees of hypoplasia of the aorta. In some cases both the ascending and transverse portions are involved to a similar degree. In others, accompanying a hypoplasia of the ascending portion, which gives off the brachiocephalic vessels, there is absence of the isthmus (coaretation of the fetal type). In these instances, the pulmonary artery leads through the ductus into the descending aorta. In others, the ascending aorta is converted into a small, thin-walled vessel which ends blindly at the base of the heart, where the coronary arteries are given off. The aortic orifice may be atretic, stenotic, or hypoplastic.

When the aortic trunk is converted into a minute vessel which does not empty into the heart, the anomaly has been called truncus solitarius pulmonalis, as differentiated from truncus arteriosus communis persistens and truncus solitarius aorticus. Although the latter two are usually associated with transposition, truncus solitarius pulmonalis may or may not be associated with transposition.

The embryologic variant in hypoplasia of the aorta without transposition is some abnormality in the primitive aortic arch system. The normal definitive aorta is derived from the ventral half of the truncus,

a small part of the fourth right aortic arch, all of the fourth left aortic arch, and the common dorsal aorta. In view of the fact that the aorta in these cases is usually normal distal to the entry of the ductus arteriosus, the anomaly is not to be looked for in the primitive common dorsal aorta. The anomaly likewise does not lie in the fourth right arch, for this would separate the brachiocephalic vessels from the ascending aorta —a condition which does not occur with this anomaly. Therefore, the following possibilities remain: (1) hypoplasia of the fourth left arch, or (2) primary abnormal spur formation between left arches four and six, leading to an abnormal aorticopulmonary septum and uneven division of the truncus. In view of the frequent absence of the isthmus with this anomaly, the first explanation is more likely. Hypoplasia of the aorta is best explained as a result of hypoplasia of the fourth left arch, resulting in unequal division of the truncus. When the anomaly is accompanied by transposition, there is, in addition, an abnormality in the absorption of the bulbus.[13]

STUDY OF THE CONDUCTION SYSTEM

Histologic study of the conduction system in both hearts revealed an increase in connective tissue in the region of the bundle of His and focal degenerative changes in the branches (the right was not found in the first case), with a focal increase in connective tissue. We are unable to say whether this increase in connective tissue in the region of the main bundle constituted an abnormality in formation or was the result of inflammatory changes. It was most likely related to the abnormal formation of the base of the aorta.

The pathologic changes may be correlated with the electrocardiograms. Both infants showed first degree auriculoventricular block (prolonged P-R interval). In Case 1, the P-R interval was 0.16 second; in Case 2, the P-R was 0.20 second. In the newborn the normal P-R duration is between 0.08 and 0.13 second.[14] The prolongation of the P-R interval was probably caused by damage to the bundle of His.

Both infants had intraventricular block. Prolongation of QRS is rare in cases of congenital heart disease.[15] In fact, Schnitker,[16] in his review of the literature, was able to find only ten cases. The QRS duration in our first case was 0.14 second; in the second, it was 0.08 second. The normal QRS duration in the newborn is between 0.04 and 0.06 second.[14] The prolongation can be accounted for by the abnormalities in the conduction system in each case, namely, increased connective tissue in the region of the bundle of His and focal degeneration and increased connective tissue in the bundle branches.

Such correlations of electrocardiographic and histopathologic studies of the conduction system are of importance in evaluating the role of the specialized muscular system in the conduction of the cardiac impulse. The recent work of Glomset and Glomset[17] and the older work of Todd[18] have questioned the role of the Purkinje system as a conducting system.

In our cases there were sufficient anatomic changes in the conduction system to account for the heart block which was present.

CONCLUSION

Two cases of aortic hypoplasia without transposition are presented, together with electrocardiographic and histopathologic studies. In these cases there was anatomic evidence of interruptions in the conduction system, and this probably accounted for the heart block which was present.

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FIVE-YEAR SURVIVAL AFTER PERFORATION OF INTERVENTRICULAR SEPTUM CAUSED BY CORONARY OCCLUSION: HISTOLOGIC STUDY OF KIDNEYS AFTER 350 INJECTIONS OF MERCURIAL DIURETICS

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THIS report is published for the following reasons: (1) The patient lived almost five years after acquiring a ventricular septal perforation through an area of infarction. (2) During this interval he received 350 injections, totaling about 650 c.c., of various mercurial diuretics, and, at necropsy, there was no histologic evidence of renal damage.

CASE REPORT

C. W. H., a white man, 44 years of age, was referred to us October 16, 1936, by Dr. Isaac Starr, who had just seen him for the first time. In 1935 he began to notice constriction in the middle of his chest and aching in both clavicular regions on strenuous exertion; these symptoms were relieved by rest. On September 15, 1936, after running 200 yards in a rainstorm, he had an attack of severe pain in the sternal region, epigastrium, throat, and left arm, associated with inability to get his breath. The pain persisted through the day, even at rest, and was relieved only by a hypodermic. He remained in bed thirty-six hours, and then went about his business as a real estate agent. On September 17 he had another attack of pain which lasted several hours, but from that time until we first saw him, almost a month later, he complained chiefly of dyspnea on exertion, with only occasional pain in the chest.

Examination showed a somewhat pallid, thin man, with a heart rate of 130 per minute and a blood pressure of 165/110. Systolic murmurs were heard at the apex and aortic area. There were no signs of congestive heart failure.

The erythrocyte count was 4,000,000, the hemoglobin, 75 per cent, and the leucocyte count, 12,000. The blood sedimentation rate (Cutler) was 26 mm. in one hour. The cardiac silhouette area was 30 per cent above the predicted figure (orthodiagram). The electrocardiogram showed evidences of former infarction in the posterior wall of the left ventricle (Fig. 1*A*). A diagnosis of unhealed cardiac infarction was made and the patient was sent home to bed.

On October 23, 1936, one of us (F. C. W.) saw him at his home, and at that time first noted a loud, rough, systolic murmur and thrill over the lower sternal region. The blood pressure on that day was 145/105. The blood sedimentation rate was 21 mm. in one hour (Cutler). A diagnosis of perforation through an infarcted area in the ventricular septum was made.

On November 6, 1936, hepatic and venous engorgement was noted for the first time. The blood pressure was 125/90; the pulse rate was 120 per minute; and the

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blood sedimentation rate (Cutler) was 18 mm. in one hour. On November 13, 1936, he began to have some choking at night which was relieved by sitting up; the veins and liver were more engorged. On November 23, 1936, edema of the feet was first observed. He grew steadily worse until, on December 27, 1936, he was admitted to the Hospital of the University of Pennsylvania with severe congestive heart failure. He then volunteered the information that, instead of remaining in bed at home, as we thought he had done, he had begun to work shortly after we first saw him, making as many as forty calls a day. We were unable to obtain any history to suggest exactly when his septal perforation had occurred.

At the time of this admission to the hospital, he had cyanosis, dyspnea, Cheyne-Stokes respiration, orthopnea, edema up to the costal margins, marked engorgement of the veins and liver, and ascites. He suffered recurring attacks of severe anginal pain, especially after eating. He was mildly psychotic, particularly on awaking from sleep. The blood pressure averaged 150/115, the pulse rate, 95, and the respiratory rate, 24. The erythrocyte count was 4.4 million, the hemoglobin, 81 per cent, and the leucocyte count, 8,700, with a normal differential count. The blood Wassermann reaction was negative. The urine showed a specific gravity of 1.028, an acid reaction, a trace of albumin, many hyaline casts, a few leucocytes, and no erythrocytes. The electrocardiogram was the same as before. Treatment consisted of rest, opiates, barbiturates, nitroglycerine, xanthines, ammonium nitrate, salyrgan, and digitalis. At first the output of urine was small. After a week, slow improvement began. The urine output became adequate, and the blood pressure dropped to 125/75. He went home January 16, 1937, and gradually gained strength.

For the rest of his life his legs were edematous. The edema was treated with salyrgan and mercupurin intravenously, usually the former because he preferred it. He received six to eight injections a month, at first 1 c.c. but after May 27, 1937, 2 c.c. His total dose was not accurately recorded, but from the time of his first injection, on December 30, 1936, until the time of his last, on August 18, 1941, he must have received about 350 injections and a total dose of about 650 c.c., all in the same large right antecubital vein, without extravasation or thrombosis. On one occasion he was given a mercurin suppository, but intense rectal irritation ensued, and the intravenous route was used thereafter. The diuresis produced by these drugs was quite satisfactory on almost all occasions; a loss of weight of about five pounds occurred each time. The diuresis was sometimes increased by ammonium nitrate administration and by salt restriction. However, the benefit derived from these two additional measures did not seem to the patient to be sufficient to warrant the trouble and discomfort involved in their use. Restriction of fluid intake did not seem to help much, so he abandoned it. Digitalis was given from time to time, but we saw no evidence of benefit from it, and the patient thought it made him feel worse. When he had unusually good diuresis (every second or third time he received an injection) he experienced a symptom which we had not encountered previously in any other patient. The drug was usually given about 3:00 P.M. The next morning, on arising, he experienced severe pain in the legs, located along the front of the lower leg and especially just external to the tibia. It was more marked in the left leg, which was the more edematous of the two. It lasted fifteen to twenty minutes, and was very intense. He said it felt as if someone had taken his foot and bent it forward and up to touch his knee.

Despite the long continued use of mercurial diuretics the patient never showed obvious clinical evidence of renal damage. The urine throughout showed a trace of albumin and sometimes a number of hyaline casts, but nothing more than would be expected in any cardiac patient with this degree of venous engorgement. There were a few leucocytes but no erythrocytes.

During the summer of 1937, the ascites, which had been present since December, 1936, disappeared and never returned in recognizable amount. On August 10, 1937,

he experienced recurring pain in the right side of the chest and developed pleural effusion on that side. He was readmitted to the hospital August 19. The right side of the chest was tapped, and a liter of sterile, bloody fluid was obtained. With the onset of pleural effusion he developed trepopnea.[1] During this hospital admission the electrocardiogram showed nothing new, the blood sedimentation rate was 3 mm. in one hour (Cutler), and the blood cell count was essentially the same as on the previous admission. The urine was negative except for a trace of albumin. The blood urea nitrogen was 22 mg. per cent, and later fell to 16 mg. per cent. The blood sugar was 75 mg. per cent. The serum proteins were 6.7 per cent. He left the hospital August 21, 1937, but during the next sixteen months returned periodically for thoracentesis. The character of the fluid was that of an exudate, rather than a transudate. On November 7, 1937, after tapping, a pleural friction rub was heard. As time went on the fluid became less bloody, and finally became clear. On December 23, 1938, the last (sixty-first) thoracentesis was done. After that the fluid ceased to accumulate and his condition remained more or less stationary.

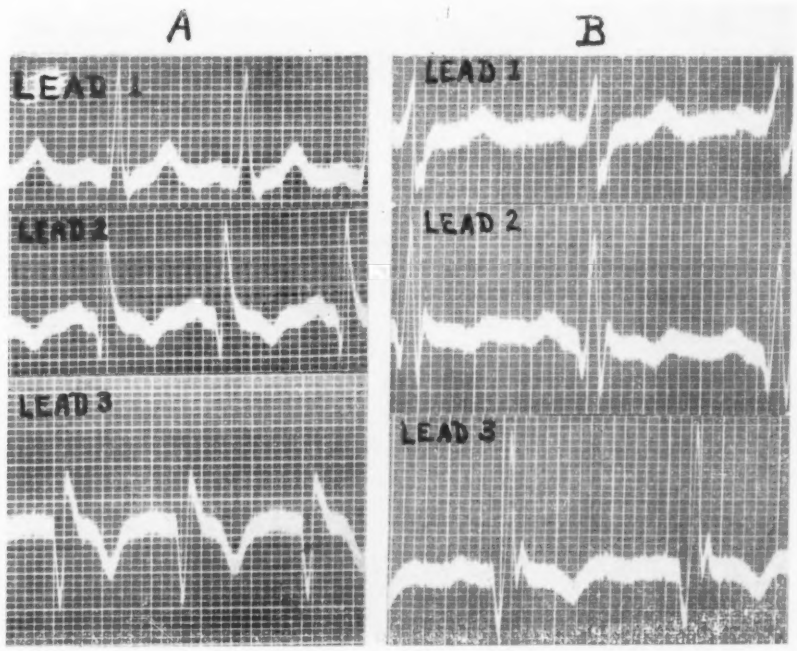

Fig. 1.—*A*. Electrocardiogram taken October 16, 1936. The QRS complexes are slurred and their duration is 0.10 second. Q waves and inverted T waves in Leads II and III indicate infarction involving the posterior wall of the left ventricle. The RS-T segment shows no deviation from the isoelectric line, but the clinical observations suggested active infarction.

B. Tracing taken August 18, 1941. The duration of the QRS complexes is 0.12 second, and a conduction defect of the right bundle branch type is present. Q_2 and Q_3 and inversion of T_2 and T_3 are still present.

The electrocardiogram throughout the last four years of his life showed signs of a healed posterior infarction, and some widening of the QRS complex suggesting a right bundle branch conduction defect (Fig. 1*B*). The heart increased in size slowly from an area of 146 sq. cm. on October 16, 1936, to 189 sq. cm. on August 18, 1941, (orthodiagram of the posteroanterior silhouette). The blood sedimentation rate remained very slow, never exceeding 3 mm. in one hour (Cutler) after the original infarct had healed.

Despite the fact that he always looked like a person in the terminal stages of cardiac failure, and despite our attempts to induce him to take adequate care of himself, he continued his occupation as a real estate agent. He worked an average of eight hours a day, traveling about the city and climbing stairs. Now and then he would indulge in unusual effort, such as chopping wood or running to avoid getting wet in the rain, which sometimes precipitated cardiac pain, intense dyspnea, dizziness, and a throbbing pain in the region of the liver. Each attack of this sort looked as if it might be his last. However, in a few days he would regain his ordinary level of chronic ill health.

During the night of August 28, 1941, he developed pain in the anterior, middle portion of the chest, which disappeared and reappeared periodically. On the evening of August 30, 1941, he had an unusually severe attack. The blood pressure dropped from its former level of 150/110 to 125/70. He was readmitted to the Medical Ward of the Hospital of the University of Pennsylvania on the service of Dr. O. H. P. Pepper at 10:00 P.M. on August 31, 1941. The blood pressure fell to 75/65, he became more cyanotic, gradually lost consciousness, and died. The clinical impression was that his death was caused by coronary insufficiency and myocardial ischemia.

The necropsy was performed by Dr. Warner F. Sheldon, twelve hours after the patient's death.

The legs were edematous; the skin of the lower part of the legs showed a brownish mottling, and appeared thin and somewhat atrophic. No intra- or extrapericardial adhesions were found. The heart weighed 840 grams. All of the valves were smooth, thin, and intact, except for small fibrous thickenings of the mitral valve leaflets. The right ventricle was markedly dilated and its walls were hypertrophied, measuring 1.0 cm. in thickness. The left ventricular wall measured 1.5 to 1.7 cm. in thickness. The left ventricular cavity showed dilatation, but proportionally less than the right ventricle. The right coronary artery was completely blocked by a firm nodule about 7 cm. from its origin, for a distance of 0.6 cm. Beyond this, the vessel was patent but small. There was an area of old infarction in the posterior, upper part of the septum and in the adjacent posterior wall of the heart. A fairly large perforation, 1.5 cm. in diameter, was found in the infarcted area of the ventricular septum. The opening into the left ventricle was easy to see; that into the right ventricle was more difficult to find because it was hidden behind a papillary muscle (See Fig. 2, *A* and *B*). The margins of the septal perforation were smooth and grayish, surrounded by fibrous tissue, and covered by endocardium. Obviously the communication was one of long standing. On the inner surface of the right ventricle, where the blood current must have struck the wall after passing through the septal perforation, there were several large, yellowish-gray, elevated plaques, each 1 × 2 cm. In the posterior, upper, left ventricular wall, adjoining the ventricular septum, there was an aneurysmal bulge 4 cm. in diameter; its outer wall was 1 mm. in thickness.

There were no other coronary occlusions and no fresh thromboses were found. The left anterior descending coronary artery was small, and some of its branches showed a few yellow plaques. The left circumflex artery was small, and its walls were smooth and thin.

The lungs showed passive congestion. One healed tuberculous nodule was found in the right upper lobe. There was evidence of former pleurisy on the right side. The pulmonary arteries were prominent, definitely dilated, and their walls were thickened by yellowish-gray, atheromatous plaques. The bronchi were moist and red and contained a little mucoid material.

The liver weighed 1,960 grams. It was pale, grayish brown, and rather firm. The capsular surface was irregular but not nodular. It cut with difficulty, and surfaces made by cutting were pale and yellowish-brown and showed indistinct lobular markings. The hepatic veins were much larger and more prominent than normal. The gall bladder and bile ducts were normal.

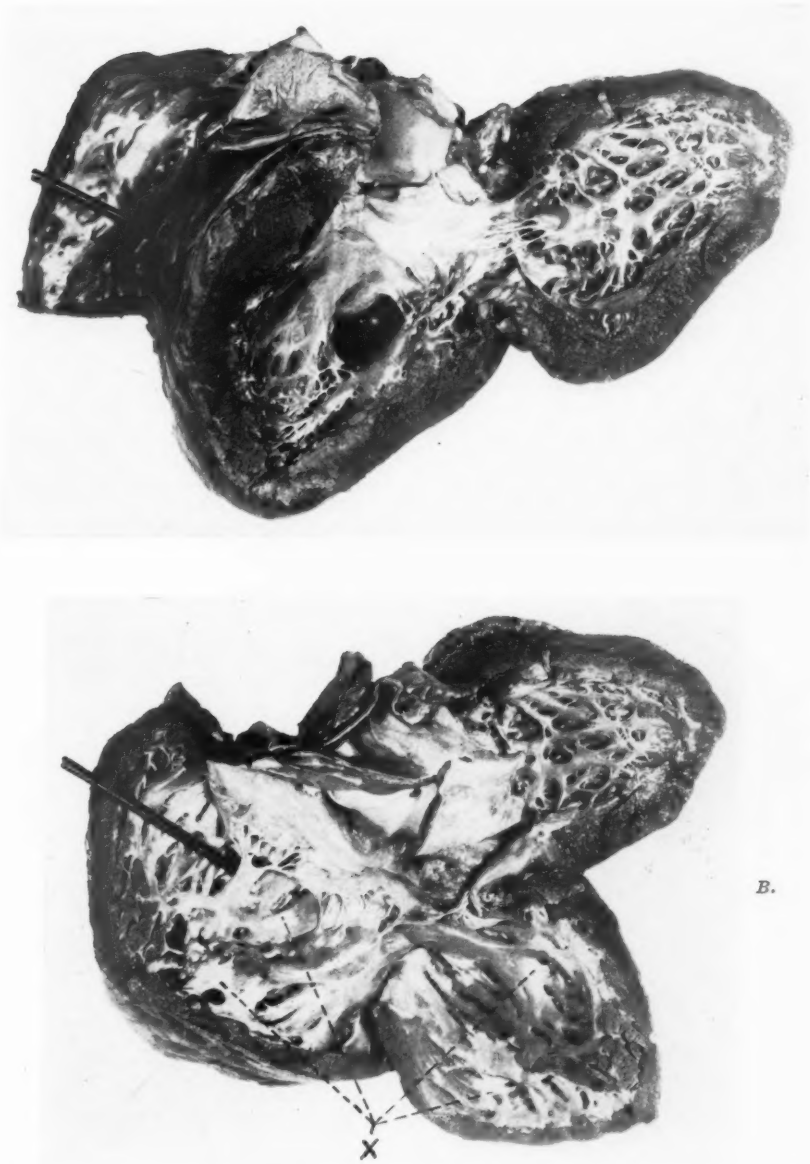

Fig. 2.—*A*. Heart of C. W. H., with left ventricular cavity exposed to view. The aortic valve is seen above, the mitral valve lies below it. Beneath the mitral valve there is a dark area, roughly 1 x 2 cm. This is an opening into the aneurysm of the posterior wall of the left ventricle, which lies behind the papillary muscle and is formed in part by the ventricular septum. The probe passes through the septal perforation, which enters the aneurysm, and its tip is visible as a shiny spot in the center of the dark area. Note the thickening of the left ventricular wall.

B. The right ventricular cavity opened, with a probe inserted behind a papillary muscle into the opening of the septal defect. "X" indicates the plaques observed where the blood current flowing through the septal defect probably struck the endocardium of the right ventricle.

The kidneys were of normal size, shape, and consistency. The left weighed 160 grams; the right, 140 grams. The capsule stripped with ease, revealing an evenly granular, dark blue surface. The cut surface was dark bluish red and bloody. The cortex was dark blue and the differentiation poor. The pelves, ureters, and bladder were normal.

Many of the organs showed chronic passive congestion, but in other respects were not remarkable.

Histologic Studies.—The larger arteries in the kidneys showed fibrous intimal thickening. The afferent vessels and the remainder of the kidney tissue were normal. Dr. Balduin Lucke, after making a careful examination of the renal tissue, stated that he saw no histologic evidence that the long continued administration of mercurial diuretics had caused kidney damage in this patient (Fig. 3). The liver was the seat of early portal cirrhosis. The lungs showed numerous clumps of phagocytic, brownish, pigmented cells in the alveoli, and some recent hemorrhages. The arterial walls were considerably thickened, both by intimal fibrous plaques and muscular hypertrophy. This arterial change varied considerably from vessel to vessel. The diaphragmatic pleura on the right side showed dense fibrous scarring, with numerous dilated vessels.

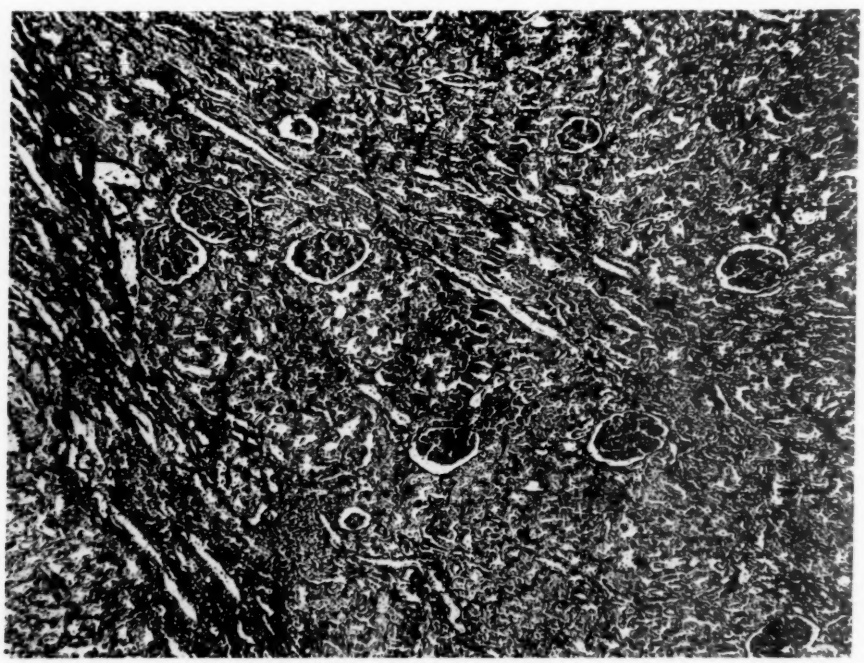

Fig. 3.—Photomicrograph of section of kidney (X37) of C. W. H. No histologic evidence of renal damage was found, despite the prolonged administration of mercurial diuretics.

Heart.—A section from the septum at the edge of the aneurysm showed complete destruction of the muscle and replacement by a narrow band of dense hyaline scar tissue. A little further from the perforation the septum showed large patches of scar tissue between hypertrophied muscle fibers. The scar contained numerous, dilated capillaries. A section from the apex of the left ventricle showed only scattered, small scars. A section from the right ventricle, made through one of the thickened endocardial plaques, showed that these structures were dense, relatively

acellular, hyaline and faintly fibrillar, collagenous scar tissue, confined to the endocardial surface, not extending into the muscle. They were apparently produced by the abnormal blood current striking the endocardium, and were obviously not overlying any areas of myocardial infarction.

In conclusion, the autopsy observations were in keeping with the clinical opinion that the infarct and perforation of the posterior part of the septum occurred at or about the time of the attack in the autumn of 1936, four years and ten months before the patient's death.

DISCUSSION

We have found references to thirty-six cases of interventricular septal perforation through an area of infarction.[2-19] Since Sager's[2] excellent review, a greater number of reports have appeared, and in more cases the diagnosis is being made ante mortem. In seven cases, so far as we know, the condition was diagnosed during the patient's life.[5, 12, 13, 15-17, 19] As a rule, the diagnosis is relatively easy to make. When a patient with a recent cardiac infarction develops a loud, rough, systolic murmur and thrill in the lower sternal region, which had not been present before, the chance that an acquired septal perforation has occurred is great. Usually there is an attack, or some abrupt change for the worse in the patient's condition, to signal the moment of the perforation, although we could not ascertain the exact time in our case. There are only three possible difficulties, of which we are aware, in making the diagnosis: (1) A patient with a congenital interventricular septal defect, who subsequently developed a cardiac infarct, if not seen prior to the infarction, might be thought to have acquired the septal performation through an infarcted area. (2) Rupture of a papillary muscle after cardiac infarction might conceivably produce a murmur which could be confused with that of an acquired septal perforation (Brunn,[16] Case I). We have never seen an example of this lesion, but Voigt[20] has published a complete review of all the nine known cases. Eight of these were probably the result of cardiac infarction. In four of the nine cases reported by Voigt there were no striking auscultatory abnormalities. (3) In certain patients with coronary thrombosis and septal perforation and with marked depression of the circulation, the murmur may be absent (Bickel and Mozer,[3] Case 2) or not very loud, and the thrill may be absent.

The location of the recent infarct in the majority of the reported cases was in the anterior surface of the left ventricle. The subject of this case report is one of the few with posterior infarction. We know of only five others in which septal perforation occurred as a result of posterior infarction.[3, 10, 13, 16, 18]

The duration of life in these cases is usually very short after the septal perforation takes place. Only seven of the reported patients are thought to have lived more than a month,[6, 9, 11, 12 15, 17, 19] and none of these is known definitely to have lived as long as a year. Therefore, our patient, who lived four years and ten months after the development of signs of septal perforation, survived at least four years longer than any other

patient of whom we are aware. He was a relatively young man who had an occlusion of the right coronary artery, but, subsequent to the original attack, he had no further coronary thrombosis. The fact that a fairly small part of his myocardium was damaged may account for his long survival.

Stern's[10] patient was the only other one to whom we could find reference in the literature with a right bundle branch conduction defect. This may have been caused by damage to the right branch of the bundle of His as a result of the infarction and septal perforation.

All patients who have survived an acquired septal perforation for any length of time have shown "right ventricular" failure, of which the outstanding features are cyanosis, edema, hepatic and venous engorgement, and often ascites.

There are a number of reports in the literature of long continued administration of mercurial diuretics without clinical evidence of renal damage.[21-28] The reports with necropsy study of the kidneys are relatively few, and the amounts of diuretic received are relatively less (240 c.c., maximum).[29, 30] We have not made a complete survey of the literature, but we have not encountered a report of any patient who received as much as our patient did and who subsequently came to necropsy.* He had about 350 injections, and a total amount of about 650 c.c., over a period of four and a half years, and, at necropsy, showed no evidence of renal damage.

SUMMARY

The patient described in this report had coronary occlusion in 1936, at the age of forty-four, and perforation of the ventricular septum through the infarcted area; he lived four years and ten months after this complication occurred. He led a fairly active existence during that time, despite continued congestive heart failure. He received approximately 650 c.c. of mercurial diuretics to control edema. No evidence of renal damage was found at necropsy.

We wish to express our appreciation to Dr. Balduin Lucke and to Dr. Warner F. Sheldon for making the pathologic studies described in this report.

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*On March 23, 1942, Dr. William G. Leaman reported a case before the Section on Medicine, College of Physicians, Philadelphia, in which the patient received 437 injections of mercurial diuretics, 2 c.c. each time, over a period of seven years, and, at necropsy, showed no evidence of mercurial damage to the kidneys.

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THE EFFECTS OF POSTURE ON THE VELOCITY OF BLOOD FLOW FROM ARM TO TONGUE

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A MARKED divergence of opinion exists as to the effects of posture on the velocity of blood flow and on cardiac output. Thompson Alper, and Thompson,[1] employing brilliant vital red, observed a pronounced increase in both the arm-to-foot and foot-to-arm circulation times in the standing-still posture, as compared to the recumbent position. Further, when they produced moderate venous congestion in a lower extremity by the application of a tourniquet, with the subject in the recumbent position, the appearance of the dye was delayed to approximately the same degree as in the standing-still position. Bock, Dill, and Edwards[2] found that the histamine circulation time (ankle-to-face) in the standing position was 1½ to 4½ times greater than in the recumbent position. Mayerson, Sweeney, and Toth,[3] who studied eleven normal male subjects, observed a marked increase in circulation time when the subject was tilted passively from the horizontal position to an angle of 75° with the horizontal; the testing agent[4] was injected into the foot vein. However, in those instances in which the agent was injected into the antecubital vein, their results were equivocal. Kvale and Allen[5] noted a longer arm-to-foot circulation time[4] in the upright posture than in the recumbent position, but the arm-to-tongue results were variable, i.e., the time was increased in 4 subjects, reduced in three, and unchanged in one. More recently, Main and Baker[6] found no significant difference in arm-to-tongue circulation time (calcium gluconate) between the recumbent and standing positions in eleven subjects.

In accord with the observation that there is a reduction in velocity of blood flow in the upright posture, many investigators[7-13] have found that the minute cardiac output is reduced in the upright posture. Conversely, the contention of some workers[14, 15,16] that posture exerts no influence on cardiac output would tend to support those studies in which blood velocity was found to be unaffected by changes in posture.

The present study was undertaken to compare the arm-to-tongue time in two positions, namely, with the body horizontal, and with the legs dependent.

METHOD

Twenty-one male and three female subjects between the ages of 20 and 72 years were studied. All but one were either free of heart disease or exhibited no clinical evidence of congestive heart failure; the exception had slight signs of congestion.

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Each subject rested 10 to 15 minutes in the recumbent (horizontal) position. The circulation time from an antecubital vein to the tongue was then measured with calcium gluconate,* using 4 c.c. of solution. The subject was then propped up in a comfortable sitting position, with both legs dependent over the edge of the bed; care was taken that muscular effort be avoided or kept at a minimum during the change of position. After another 10 to 15 minutes' rest, the circulation time was again measured. The patient was then returned to the previous recumbent position, and, after another rest of 10 to 15 minutes, a third measurement was made. All injections were made into the antecubital vein at the level of the right auricle. A total of 73 measurements was taken; a fourth test was made in one case as a check (40 minutes after the third measurement) because of a series of unexpectedly high figures.

RESULTS

The circulation time was greater in the sitting, legs-dependent position than in the recumbent position in 15 subjects, less in 7, and equivocal in 2. Of the 15 subjects who had a longer circulation time in the sitting, legs-dependent position, 12 showed an average recumbent circulation time within the normal limits of 8 to 16 seconds, and 3 exceeded 16 seconds. Of the 7 subjects whose circulation time was less in the sitting, legs-dependent position, 5 had an average recumbent time greater than 16 seconds (2 of these were subjects with auricular fibrillation without demonstrable congestion), and 2 exhibited a normal recumbent time. In the 2 instances in which the results were indefinite, the average recumbent time was normal.

DISCUSSION

Some of the slight changes in circulation time between the recumbent and the sitting, legs-dependent position were probably within the limits of experimental error. However, in many cases the figures were sufficiently different to indicate changes outside the experimental error, especially since the effect was reversible. Even the slight changes in circulation time in some of our patients were probably real because they were also reversible, but the fact that the differences sometimes approached the experimental error makes the results less striking and may explain some of the differences between our results and those previously reported. The contradictory observations in some previous reports may also have been the result of failure in some cases to consider the fact that in the standing position there are increased muscular tone and swaying which exert a milking action on the venous reservoirs, so that there is less pooling than occurs in the sitting, legs-dependent position.

However, some of the differences are the resultant of two opposite effects of the change in posture on circulation time, namely, (a) a reduction in the venous return in the sitting, legs-dependent posture, and (b) a narrowing of the vascular bed between the point of injection and

*A 20 per cent solution of calcium gluconogalactogluconate (Neo-Calglucon) was generously supplied by the Sandoz Chemical Works.

TABLE I

SUBJECTS WITH INCREASED CIRCULATION TIME IN SITTING, LEGS-DEPENDENT POSITION

NO.	SUBJECT	AGE YEARS	DIAGNOSIS	RECUMBENT SEC.	SITTING, LEGS-DEPENDENT SEC.	RECUMBENT SEC.
			I. Subjects With Normal Average Recumbent Time			
1.	E. A.	36	Diabetes mellitus	12.7	16.4	12.2
2.	C. C.	38	Cholecystitis	12.8	16.5	14.7
3.	S. S.	42	Diagnosis undetermined (No cardiac disease)	15.3	20.0	16.2
4.	E. L.	35	Diagnosis undetermined (No cardiac disease)	12.7	17.4	12.8
5.	R. J.	45	Hemorrhoids; hernia	14.3	15.4	12.2
6.	J. N.	44	Old (3 years) healed myocardial infaret	11.0	13.2	12.0
7.	A. V.	33	Anorexia and weakness of undetermined etiology (No cardiac disease)	10.8	11.9	10.4
8.	E. V.	35	Amebiasis	10.3	11.3	9.7
9.	J. S.	41	Pneumonia (recovered)	10.8	12.4	11.7
10.	F. K.	37	Epilepsy	13.4	14.7	13.9
11.	M. S.	20	Chronic ulcerative colitis	11.0	11.7	10.3
12.	S. B.	66	Anal fistula	13.5	15.2	15.0
			II. Subjects With Prolonged Average Recumbent Time			
1.	I. K.	54	Beriberi heart disease (treated)	16.0	17.0	16.2
2.	P. H.	45	Pneumonia (recovered)	18.0	19.6	16.0
3.	L. R.	48	Arteriosclerotic heart disease Diabetes mellitus Early signs of congestive failure	20.0	23.8	15.1

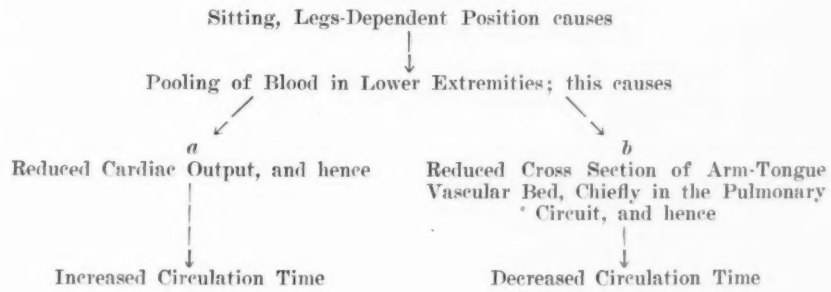
TABLE II

SUBJECTS WITH DECREASED CIRCULATION TIME IN SITTING, LEGS-DEPENDENT POSITION

NO.	SUBJECT	AGE YEARS	DIAGNOSIS	RECUMBENT SEC.	SITTING, LEGS-DEPENDENT SEC.	RECUMBENT SEC.
			I. Subjects With Normal Average Recumbent Time			
1.	L. S.	33	Hernia	12.4	10.6	11.8
2.	H. C.	50	Rheumatoid arthritis	12.4	10.1	10.7
			II. Subjects With Prolonged Average Recumbent Time			
1.	S. B.	72	Arteriosclerotic heart disease, auricular fibrillation. (No clinical evidence of congestion)	26.0	22.4	29.6
2.	L. M.	69	Arteriosclerotic heart disease (Noncongestive) Diabetes mellitus	16.3	13.9	16.4
3.	J. M.	58	Angina pectoris (No clinical evidence of congestion)	21.4	18.6 Recumbent repeated 40 min. later 24.8	25.0
4.	L. B.	53	Neuritis? (No clinical evidence of congestion, or heart disease)	18.4	16.8	17.3
5.	N. M.	52	Auricular fibrillation, etiology undetermined. (No clinical evidence of congestion)	18.0	16.4	17.2

the point of response, especially in the pulmonary bed. It would appear that in health the effect of mechanism *a* (Diagram I) predominates, but not always sufficiently to neutralize the effect of mechanism *b*. In congestive heart failure, whether recognizable or not, with its increase in circulating blood volume, the effect of mechanism *b* appears to predominate usually.

Diagram I



The results of this study offer an objective measure of the diminution of pulmonary engorgement brought about by the supine posture, with legs dependent, in cases of orthopnea. The spontaneous tendency of patients with congestive failure to assume the legs-dependent position at the edge of the bed is probably explained by the fact that this position lessens pooling of blood in the lungs. Our results support the contention that a reduction in minute cardiac output and pulmonary stasis occurs in the upright posture, incident to a diminution in circulating blood volume[17] caused by pooling of blood in the lower extremities.[18] When there is congestion of the lungs, the latter effect dominates; otherwise, the former tends to be the more prominent.

SUMMARY AND CONCLUSIONS

Circulation time studies by the calcium gluconate arm-to-tongue method indicate that when the circulation time in the recumbent position is normal, the values in the sitting, legs-dependent position (which eliminates to a large extent the muscular contractions and swaying incident to standing) tend to be higher than in the recumbent position. However, when the circulation time in the recumbent position is prolonged, the circulation time in the upright position tends to be lower. This substantiates the observations that minute cardiac output is less in the sitting and standing positions than in the recumbent position. However, the decrease in the pulmonary bed on changing from the recumbent to the upright position is apparently relatively greater in patients with congestive heart failure than in normal persons.

I wish to express my appreciation to Dr. L. N. Katz, under whose guidance this study was undertaken, for his valuable advice and criticism.

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THE USE OF PAPAVERINE AS AN OBJECTIVE MEASURE OF CIRCULATION TIME

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DESPITE the development and application of numerous methods for measuring circulation time in man,[1, 2] there are few that are simple, reliable, and objective. In the course of clinical studies of papaverine hydrochloride, a sudden deepening of respiration shortly after injection was almost uniformly noted; this observation suggested that this drug might be used to obtain an objective measure of circulation time. This report presents a discussion of the method evolved and the results obtained in normal and in some abnormal states.

TECHNIQUE

After preliminary tests, the following technique was established. The patient lies supine in a quiet room for at least five minutes before the test is performed. He is informed about what will probably occur and asked to refrain from coughing, sighing, or voluntarily taking a deep breath. The pulse and respiratory rate are noted, and particular attention is paid to the depth and character of the respiration (intercostal and abdominal breathing), so that changes may be quickly observed. The antecubital vein is used for injection, and for this purpose the arm is placed on a pillow so that the level of the site of injection is about 10 cm. above the posterior axillary line. A 2 c.c. Luer syringe and a 20-gauge needle are employed for the injection. About ten seconds are allowed to elapse between insertion of the needle and injection of the drug in order to circumvent the circulatory effects of the prick of the needle and the venous congestion produced by the tourniquet. The papaverine hydrochloride† is injected within one second, and the circulation time is clocked with a stop watch in the usual way. The end point will be described below.

End Point.—The end point is similar to that observed by Robb and Weiss[3] with the sodium cyanide method. It is signalled by a sudden, deep inspiration, with employment of the abdominal muscles, which interrupts the usual phase of respiration, and is at times accompanied by a sigh or gentle exclamation. This is commonly followed by visible flushing of the face or cheeks, or a feeling of facial warmth, a sensation of throbbing in the temples, mild dizziness, and, less frequently, acceleration of the heart. The tachypnea lasts fifteen to sixty seconds, averaging about thirty seconds. It is usually not distressing, and the other symptoms are well tolerated when the recommended dose is used. The end point is sharp and easily recognized. In dyspneic patients it is manifested by a sudden, deep inspiration, together with full use of the intercostal muscles, especially the upper ones.

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Dosage.—After extensive preliminary trials we found that 40 mg. (1.25 c.c.) was the most satisfactory dose; it uniformly gives a sharp end point with a minimum of side reactions. A dose of 32 mg. (1.00 c.c.) may be used successfully, but occasionally we have obtained no end point with it or one that is not easy to distinguish.

That the circulation time was not significantly affected by the amounts used was shown by duplicate measurements on two patients with increasing doses of papaverine hydrochloride, viz., 32, 40, 48, and 56 mg. These amounts were injected at two to ten minute intervals. As shown in Table I, the result was not significantly changed with doses between 32 and 56 mg.* With 48 mg. or more the tachypnea becomes distressing, and the patient complains of feeling "knocked-out"; in addition, headache and a general feeling of weakness may ensue.

TABLE I

EFFECT OF INCREASING DOSES OF PAPAVERINE ON THE CIRCULATION TIME

SUBJECT	DOSE OF PAPAVERINE (MG.)	TIME OF END POINT (SEC.)
1. P. H.	32	25.4
	40	27.0
	48	22.6
	56	21.4
2. L. K.	32	24.8
	40	24.2
	48	24.2
	56	21.6

With doses of 40 mg., duplicate tests may be made at two to five minute intervals without untoward symptoms or a change in the circulation time (Table II). Papaverine is not irritating locally and does not cause necrosis.

RESULTS

Fifty patients,† selected at random, were studied. This group included some patients with heart disease, but without any subjective or objective manifestations of heart failure. There were 41 men and 9 women, and their weights varied from 100 to 200 pounds. The distribution according to age was as follows: 8 were between 15 and 20, 5 between 20 and 30, 9 between 30 and 40, 10 between 40 and 50, 10 between 50 and 60, and 8 between 60 and 70 years of age.

The range of values for the circulation time with papaverine varied from 15.4 to 27.0 seconds; the average was 20.8 seconds.

In 24 of these patients duplicate measurements were done at 2 to 5 minute intervals (Table II). As shown in this table, the reproducibility of the results was good; the range of differences between any two measurements was 0 to 3.0 seconds, and the average, 1.2 seconds.

Table III and Table IV list the data on 6 patients with congestive heart failure and 4 patients with clinical and laboratory evidence of hyperthyroidism, respectively. Measurements with decholin were also made on the former at the same time. In patients with heart failure

*The difference in results with these two doses in subject P. H. was only one second greater than the range of variation after duplicate measurements with the same dose (see Table II).

†Normal in the sense defined by Robb and Weiss.[3]

TABLE II

DUPLICATE MEASUREMENTS OF PAPAVERINE CIRCULATION TIME

SUBJECT	DOSE OF PAPAVERINE MG.	TIME OF END POINT SEC.	DIFFERENCE SEC.
1. H. P.	40	24.2	0.6
	40	24.8	
2. I. K.	40	22.4	0.4
	40	22.0	
3. M. L.	40	19.4	1.6
	40	21.0	
4. C. W.	32	25.4	0.6
	32	26.0	
5. M. W.	40	18.0	0.6
	40	17.4	
6. H. L.	40	27.0	2.0
	40	25.0	
7. J. LaF.	40	21.2	0.4
	32	21.6	
8. S. R.	40	15.4	1.0
	40	16.4	
9. T. F.	64	17.2	0.8
	64	18.0	
10. V. W.	64	17.5	1.5
	64	19.0	
11. I. V.	40	26.8	1.3
	40	25.5	
12. A. W.	40	18.6	2.4
	48	21.0	
13. H. C.	64	17.2	3.0
	64	20.2	
14. R. R.	40	21.6	0.6
	40	21.0	
15. F. D.	40	20.8	0.4
	40	20.4	
16. H. M.	32	19.2	1.4
	48	20.6	
17. J. D.	48	17.6	1.0
	56	16.6	
18. H. W.	32	17.8	1.2
	48	19.0	
19. E. L.	32	17.4	1.4
	48	18.8	
20. H. W.	40	20.2	1.2
	40	21.4	
21. W. R.	40	26.8	0
	40	26.8	
22. W. D.	40	17.0	2.0
	40	19.0	
23. J. M.	40	17.0	1.2
	40	18.2	
24. P. H.	40	24.2	0.6
	40	24.8	

Range of variation between two successive readings is 0 to 3.0 sec.
Average difference is 1.2 sec.

the papaverine circulation time, as well as the decholin time, was markedly prolonged. Patient R. C. was of particular interest. His papaverine circulation time when he did not have failure was 18.4 seconds. One month later he developed dyspnea, orthopnea, cyanosis, and basal râles, indicating acute heart failure. The papaverine test at this time revealed a circulation time of 60 seconds (the decholin time was 33 seconds); this confirmed the diagnosis of heart failure. The papaverine circulation time in hyperthyroidism is shortened, but the deviation from normal is not as marked as its prolongation in heart failure.

TABLE III

CIRCULATION TIME IN CONGESTIVE HEART FAILURE

PATIENT	ETIOLOGIC DIAGNOSIS	RESPIRATORY RATE PER MIN.	PULSE RATE PER MIN.	TEST SUBSTANCE	TIME OF END POINT SEC.
1. S. R.	Syphilitic heart disease	30	92	Papaverine	50.2
2. W. H.	Rheumatic and hypertensive heart disease	20	80	Papaverine Decholin	38.6 30.8
3. J. C.	Syphilitic heart disease	38	112	Papaverine Decholin	48.0 30.8
4. T. G.	Possibly beriberi heart disease	38	80	Papaverine Decholin	115.8 63.6
5. F. M.	Arteriosclerotic heart disease	22	92	Papaverine	60.4
6. R. C.*	Arteriosclerotic heart disease	32	92	Papaverine Decholin	60 33

*Discussed in text.
Range of papaverine circulation time is 38.6 to 115.8 sec.
Range of decholin circulation time is 30.8 to 63.6 sec.

TABLE IV

CIRCULATION TIME IN HYPERTHYROIDISM

PATIENT	BASAL METABOLIC RATE	PULSE RATE PER MIN.	TEST SUBSTANCE	TIME OF END POINT SEC.
1. I. S.	+26	108	Papaverine	13.3
2. L. D.	+6	100	Papaverine Decholin	13.8 8.8
3. R. P.	+19	132	Papaverine	13.4
4. L. B.	+34	100	Papaverine	11.7

The results obtained with papaverine in the control series were compared with those of a subjective test, in which 4 or 5 c.c. of a 20 per cent calcium gluconate* solution were used; this test was done either shortly before or after the papaverine test, or within one to two days of the latter. The values obtained in 18 patients are presented in Table V, which shows that the calcium gluconate circulation time differs from the papaverine time by 0.6 to 12.4 seconds. The fact that

*Neo-Calglucon, which was kindly supplied by Sandoz and Company.

the former estimations are within the normal range further indicates that there was no circulatory failure in the patients studied.

TABLE V

COMPARISON OF PAPAVERINE AND CALCIUM CIRCULATION TIMES

SUBJECT	TEST SUBSTANCE	TIME OF END POINT
1. S. R.	Papaverine	15.9
	Calcium	13.7
2. P. H.	Papaverine	24.8
	Calcium	18.0
3. J. D.	Papaverine	17.6
	Calcium	14.0
4. E. M. L.	Papaverine	17.4
	Calcium	12.8
5. A. T.	Papaverine	21.8
	Calcium	12.4
6. C. M.	Papaverine	20.6
	Calcium	20.0
7. H. W.	Papaverine	18.4
	Calcium	15.4
8. D. D.	Papaverine	27.0
	Calcium	19.4
9. J. D.	Papaverine	15.4
	Calcium	11.2
10. H. Y.	Papaverine	15.8
	Calcium	9.0
11. J. T.	Papaverine	20.8
	Calcium	18.2
12. E. S.	Papaverine	21.2
	Calcium	12.6
13. W. N.	Papaverine	19.2
	Calcium	15.0
14. F. K.	Papaverine	22.0
	Calcium	13.4
15. S. B.	Papaverine	25.4
	Calcium	15.0
16. E. C.	Papaverine	25.0
	Calcium	16.0
17. M. G.	Papaverine	16.0
	Calcium	10.6
18. J. M.	Papaverine	26.2
	Calcium	13.8

Range of papaverine circulation time is 15.4 to 27.0 sec.
Range of calcium circulation time is 9.0 to 20.0 sec.
Range of difference between papaverine and calcium times is 0.6 to 12.4 sec.
Average difference between papaverine and calcium times is 6.1 sec.

DISCUSSION

Robb and Weiss[3] have clearly defined the requisites of any agent which is given intravenously as a measure of circulation time, namely,

it should be nontoxic in the doses employed; it should not influence the velocity of blood flow until the signal reaction has occurred; it should be quickly inactivated, so that a second measurement may be made within a few minutes; and the end point should be easily recognized. Our results show that papaverine adequately fulfills these requirements.

Papaverine hydrochloride has the advantage over sodium cyanide of being readily available in known concentrations in sterile solution, and the small volume of solution which is used can be rapidly administered.

In addition to this, papaverine hydrochloride has been used therapeutically in the treatment of conditions associated with smooth muscle spasm, as, for example, pulmonary embolism[8] and peripheral embolism.[9] Furthermore, work on animals in this laboratory has shown that papaverine hydrochloride is a potent and lasting coronary dilator,[4] that it can prevent or reduce artificially induced ventricular fibrillation,[5] and that it will abolish or diminish artificially induced ventricular premature systoles in the dog.[6] We have applied this information clinically[7] and have found that when this drug is given intravenously or orally it is efficacious in the treatment of the anginal syndrome and of premature systoles. Papaverine can also be administered intravenously as a temporary measure to abolish or reduce single or multiple ectopic premature contractions.[7] Thus, our evidence indicates that this drug may be employed intravenously for simultaneous measurement of the circulation time and attainment of some therapeutic effect which might be desired, as, for example, in pulmonary embolism. We are not aware of any therapeutic possibilities possessed by sodium cyanide.

Robb and Weiss[3] concluded, from indirect evidence in man and more direct evidence in animals, that sodium cyanide acts on the carotid sinus, and hence gives a measure of the arm-carotid sinus time. The fact that the range of our measurements, as well as the average for papaverine, is longer than that obtained with the sodium cyanide method by about five to six seconds suggests the following possibilities:

1. Papaverine has a slower effect on the carotid sinus in the dosage recommended.
2. It acts on a center more distal from the heart than the carotid sinus, i.e., the respiratory center in the medulla.

We are not acquainted with any work on the action of papaverine on the carotid sinus in animals. Macht[10] has said that papaverine apparently stimulates the respiratory center in the intact, unanesthetized rabbit. Our results with papaverine are nearer the values obtained with the histamine circulation time test (thirteen to thirty seconds, average twenty-three seconds[3]) than those with the cyanide method. Histamine[3] is believed to cause dilatation of the smaller blood vessels of the skin and brain. As previously mentioned, papaverine commonly causes visible flushing of the face. Hence, the evidence, although indi-

rect, suggests that this drug acts on a site beyond the carotid sinus, possibly on the blood vessels of the brain, or, more likely, on the respiratory center. Accordingly, for the present, at least, papaverine may be considered to offer a measure of the arm-respiratory center circulation time.

SUMMARY

1. A new, simple, reliable, and objective method, which utilizes papaverine hydrochloride intravenously, is described for the measurement of circulation time. The end point consists of a sudden, deep inspiration.

2. The recommended dose is 40 mg. (1.25 c.c.). The average time for 50 normal persons without evidence of heart failure was 20.8 seconds; the range extended from 15.4 to 27.0 seconds.

3. Duplicate measurements may be made within 2 to 5 minutes; the estimations varied by no more than 3 seconds, and the variations averaged 1.2 seconds.

4. Indirect evidence suggests that papaverine hydrochloride may measure the arm-respiratory center circulation time.

5. Whenever papaverine is given intravenously for therapeutic reasons, the circulation time may readily be measured simultaneously by means of the above technique.

It is a pleasure to acknowledge the advice and criticism of Dr. Louis N. Katz, under whose guidance this study was carried out.

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Clinical Reports

COARCTATION OF THE AORTA, WITH RUPTURE OF THE WALL BELOW THE POINT OF CONSTRICTION

Report of a Case and Review of the Literature

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IN ABBOTT'S[1] series of 200 cases of the adult type of coaretation and in Benkwitz and Hunter's[2] series of 75 cases (52 of adult type), the causes of death were: (1) cardiac decompensation, 38 per cent; (2) rupture of ascending aorta, 17 per cent; (3) cerebral lesions, 13 per cent; and (4) mycotic endarteritis, 7 per cent. In the two series combined, there were only three cases of rupture of the aorta below the constriction. Goodson,[3] in 1937, and Hecker,[4] in 1939, reported two more cases of coaretation of the aorta with rupture of the wall below the site of coaretation. Thus, in all, five cases of coaretation of the aorta, with rupture of the wall below the point of constriction, have been reported. We present another case of the same type in which there were some other interesting features.

CASE REPORT

An eleven-year-old boy was admitted to the hospital with complaints of hematemesis, dyspnea, and precordial pain.

He had measles at the age of three, but no other illnesses, accidents, or operations. The family history was negative. The boy was born at full term; delivery was easy, and growth and development had been normal.

The boy was in good health until three months before admission, when he noticed increasing dyspnea and was forced to curtail his exercise and finally stop playing entirely. He had an occasional cough and a small amount of sputum. In spite of medication he became worse, with excessive dyspnea, frequent cough, and difficulty in sleeping. One week before admission he suddenly became worse and complained of precordial pain and orthopnea. His sputum was consistently free of blood and was described as a "phlegm." The night before admission he awoke at 10:00 o'clock and vomited a large amount of coffee-ground material. Later he spat up a quantity of bright red blood. At 4:00 A.M. he again vomited blood and became unconscious. He passed a large black stool.

Physical Examination.—The patient was a well-developed but rather poorly nourished boy who appeared acutely ill. He had marked dyspnea and a remarkable pallor of the face. The hands were cold and clammy and the pulse was extremely rapid (170). Examination of the head, eyes, ears, and nose was negative.

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There was marked pallor of the buccal mucous membrane. The chest was sthenic in type and breathing was rapid. Sibilant râles were heard throughout the chest, both on inspiration and expiration. The breath sounds were bronchovesicular. Percussion was resonant throughout. The heart rate was 170 per minute and the rhythm was normal. The apex impulse was diffuse, and the outer border of cardiac dullness was in the fifth intercostal space, 8½ cm. from the midline. There was a loud systolic murmur in the aortic area, transmitted to the great vessels, and a soft systolic murmur in the mitral area, transmitted to the axilla. There was reduplication of both aortic and pulmonic second sounds. The abdomen was scaphoid and tender throughout. The liver was palpable two cm. below the costal margin, and the spleen was thought to be palpable. The extremities showed no edema, and the reflexes were normal.

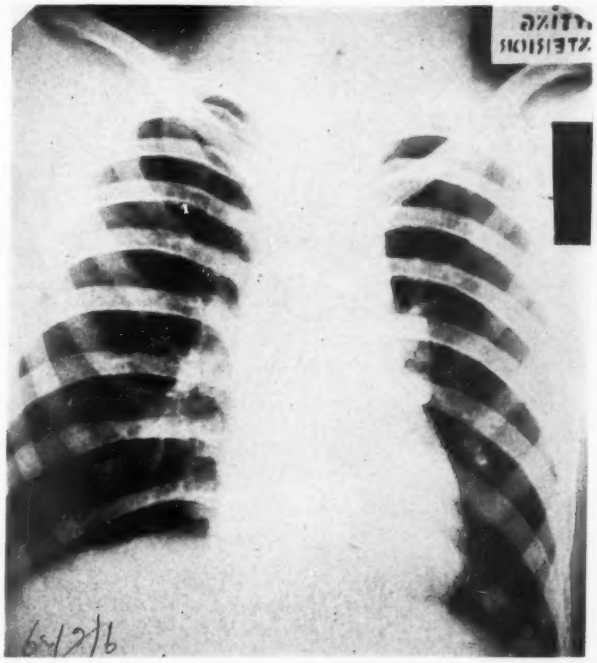

Fig. 1.—Roentgenogram of chest, showing absence of aortic knob and broadening of the aortic arch.

Laboratory Data.—The erythrocyte count was 3,310,000, the hemoglobin, 49 per cent, the leucocyte count, 35,000, and the platelet count, 299,700. The differential leucocyte count showed 3 per cent metamyelocytes, 30 per cent nonsegmented forms, 59 per cent segmented forms, 7 per cent lymphocytes, and 1 per cent monocytes. The blood sugar level was 100 mg. per cent, and the nonprotein nitrogen content of the blood was 37 mg. per cent. The blood Kahn and Kline reactions were negative. A stool culture was negative for the typhoid and dysentery group.

Roentgenologic examination of the chest showed no enlargement of the heart, but a slight broadening of the aortic arch. The lungs appeared normal (Fig. 1). The electrocardiogram showed: (1) sinus tachycardia; (2) right axis deviation; and (3) evidence of myocardial and auricular disease.

Course in Hospital.—The second day the temperature was 99° F. The patient received a transfusion of 150 c.c. of whole blood and felt better; he passed a bloody stool. The blood pressure was 155/80.

On the morning of the third day he appeared improved, had better color, and wanted to get up and walk about. Examination of the chest revealed some increase in the width of the area of aortic dullness. The blood pressure in the left arm was 150/95; and, in the right arm, 145/80. The pulse rate was 100.

In the afternoon of the third day a sudden, massive hemorrhage occurred; blood poured from the mouth and nose. He rapidly went into shock and died before any effective treatment could be administered.

Autopsy.—The body was that of a well-developed, somewhat undernourished boy of eleven years; the skin was pale, with a slight yellowish cast. No gross lesions or abnormalities were noted on external examination of the body. There was a moderate amount of thin, straw-colored fluid in both pleural cavities and in the pericardial cavity.

Fig. 2.—Marked coarctation of the aorta at the site of insertion of the ligamentum arteriosum. Anomalous vessel between the left subclavian artery and the constriction.

The heart was somewhat enlarged, particularly the left ventricle. The epicardium was thin and intact. The myocardium was pale and somewhat thickened in the left ventricle. The valves and coronary arteries were not abnormal.

Aorta.—In the aorta, one inch below the origin of the left subclavian artery, there was a marked and circumscribed narrowing of the lumen to a diameter of about 5 mm. This narrowing was at the site of insertion of the ligamentum arteriosum, which was present as a thick fibrous cord 1 cm. long. There was an anomalous vessel, 2 mm. in diameter, in the anterior wall of the aorta and 1 cm. below the left subclavian artery (Fig. 2). Just below the coarctation there was an aneurysmal dilatation along the anterior wall of the aorta, with rupture into the esophagus. On the line of rupture there was a vegetation 3 mm. long, and, in the opening, there was a large, partially organized thrombus that protruded into the esophagus (Fig. 3). The lungs revealed some hypostatic congestion and the gastrointestinal tract contained a large amount of dark, partially digested blood.

Microscopic Examination.—Sections from the aorta at the site of rupture showed a vegetation formed by fibrin, inflammatory cells, and granulation tissue, but no bacteria were present. The layers of the wall showed infiltration with inflammatory cells, mostly neutrophiles and monocytes. The thrombus between the aorta and esophagus showed partial organization, with many fibroblasts throughout. The heart muscle showed some edema and also hyperplasia of the fibers. Moderate congestion and edema were present in the lungs. The kidneys revealed lesions of an embolic type, with localized collections of inflammatory cells around some of the glomeruli, and also some glomeruli with obliteration of Bowman's capsule.

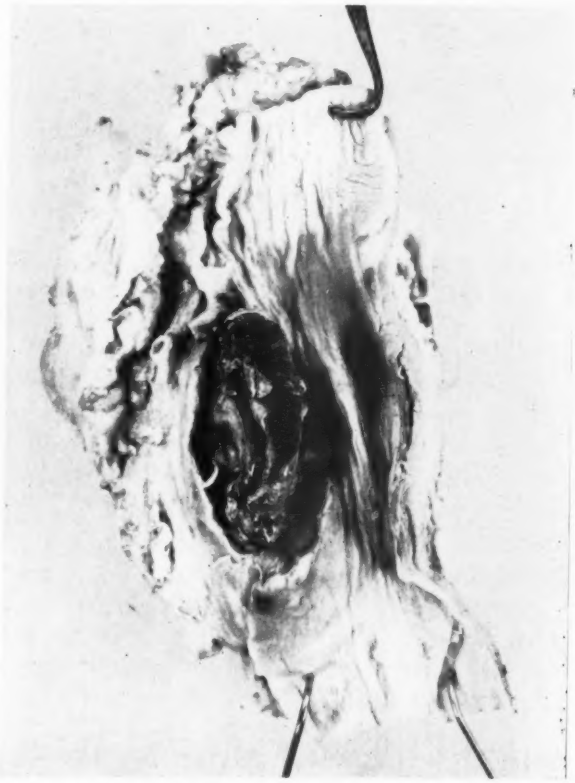

Fig. 3.—Large thrombus protruding into the esophagus through a break in the mucosa.

The five cases of coarctation of the aorta, with rupture of the wall below the point of constriction, that have been previously published are summarized here briefly. The description of the first three cases[5-7] is taken from Abbott.[1]

Leudet,[5] in 1858, reported the case of a woman, thirty-seven years old, who had had dyspnea, dysphagia, pain in the left side of the chest, and edema of the extremities for nineteen months. She died suddenly after vomiting a large quantity of blood. The descending aorta just below the origin of the left subclavian was so extremely constricted that it would admit only a blunt probe, and, just below this point, presented a huge, irregular, aneurysmal dilatation lined by osseous and car-

tilaginous plaques which opened freely into the left bronchus. A good collateral circulation was present, and also some enlargement of the left ventricle.

In 1878, Kriegk[6] published the case of a university professor, aged forty-eight, who had suffered for several years from precordial pain and anxiety; he died suddenly while going to bed. The autopsy revealed much blood in the mediastinum and in the left pleura. At the site of entrance of the obliterated duct, the descending aorta was narrowed by an annular constriction which admitted the little finger. On either side of this constriction there was a double intimal tear. The tear above the stenosis was 1.5 cm. long and ran around the aorta parallel to the ridge; that below was of similar length and course and led into a dissecting aneurysm which had extended downward as far as the celiac axis; both tears had ruptured near their origin into the mediastinum and adjacent structures.

In 1907, Mönckeberg[7] presented the case of a woman, aged twenty-six, with congenital hypoplasia of the aorta. The aorta narrowed rapidly distal to the origin of the innominate artery and became reduced at the insertion of the obliterated ductus to a circumference of 1.3 cm. Just below the stenosis there began an aneurysmal dilatation which bulged into the left lung; it measured 8 cm. in its greatest vertical diameter. The ligamentum arteriosum was a solid cord, 1.5 cm. long, attached to the floor of a funnel-shaped, loculated pocket which had perforated into the left pleura. There was a large collateral circulation.

Goodson,[3] in 1937, recorded the case of a boy, sixteen and a half years old, who had had dyspnea and precordial pain for two months before entering the hospital. He died suddenly, three weeks later, after having expectorated bright red, frothy blood on several occasions. The autopsy revealed narrowing of the descending arch of the aorta to 1 cm. at about 1 cm. above the insertion of the ductus arteriosus, which was patent for about half its length. Immediately below this insertion there was a fibrous constriction of the aortic wall to a lumen 3 mm. in diameter. Two centimeters below the coaretation there was an 8 mm. opening into an aneurysm which was situated on the left of the midline between the fifth and sixth ribs and measured 3.5 by 3.5 by 4 cm. It was partly filled with organizing clot and had ruptured into a small bronchus.

In 1939, Hecker[4] reported the case of a man, sixty-two years old, who had had hypertension for years. After a strenuous movement to prevent falling from his seat, he suddenly developed a severe, lancinating pain in the back. He died two weeks later of self-inflicted gunshot wounds. The autopsy revealed a marked constriction of the descending arch of the aorta one and one-half inches beyond the origin of the left subclavian artery. At this point a ligamentous attachment, about one-fourth to one-half inch in width, extended to the pulmonary artery. The lumen

of the aorta at the coarctation was about 2 mm. in diameter. Immediately below this point the aorta became enlarged and bulbous. About six inches below the constriction there was a longitudinal slit through the posterior wall of the aorta. Through this opening the blood had dissected between the walls of the aorta upward to the constriction and downward to within about one and one-half inches of the bifurcation of the abdominal aorta.

DISCUSSION

In the case that we have presented here, as in that of Hamilton and Abbott,[8] there was an anomalous vessel between the origin of the left subclavian artery and the site of coarctation. We agree with Hamilton and Abbott that an anomalous vessel in this location lends support to the views of Reynaud,[9] Rokitansky,[10] and Loriga,[11] to the effect that coarctation is caused by an abnormal development during embryonic life, localized at the point of junction of the fourth, fifth, and sixth left aortic arches. The anomalous vessel would represent persistence of the (evanescent) fifth left arch.

Rupture of the ascending aorta is much more common in coarctation than rupture of the wall below the constriction. This can be easily explained by the fact that the blood pressure is much higher above than below the constriction. The explanation of rupture below the site of coarctation may be found in a certain weakening of the wall near that point. We believe, however, that back pressure from some strain, with or without contraction of the abdominal muscles, will give a very marked rise in blood pressure against a rather rigid wall near the site of coarctation and may produce a tear of the wall. Hecker's[4] case seems to illustrate this back pressure idea.

SUMMARY

1. A case of coarctation of the aorta, with rupture of the wall below the point of constriction, into the esophagus, is presented.

2. The five previously published cases of coarctation with rupture of the wall below the constriction are reviewed.

3. We believe that back pressure plays an important role in the mechanism of rupture of the wall below the site of coarctation.

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THE PERIPHERAL BLOOD FLOW IN A CASE OF ADRENAL PHEOCHROMOCYTOMA BEFORE AND AFTER OPERATION

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THE clinical diagnosis of adrenal pheochromocytoma has been made with increasing frequency during recent years. The syndrome associated with the paroxysmal hypertension of adrenal medullary tumors was first clearly described by Labbe, Tinel, and Doumer, in 1922.[1] Beer, King, and Prinzmetal[2] demonstrated during the hypertensive crises the presence of a circulating pressor substance, and identified it as adrenalin. This substance was no longer present after operation. Landis, Montgomery, and Sparkman[3] found that the intravenous administration of epinephrine was followed by an elevation of blood pressure, a decrease in peripheral blood flow and skin temperature, and an increase in peripheral resistance.

We have had the opportunity to make measurements of the peripheral blood flow before operation and on several occasions after operation on one patient with a chromaffin cell tumor of the adrenal medulla;† such observations have not previously been recorded. In order to have other data for correlation in this patient, the basal metabolic rate, blood pressure, pulse rate, and circulation time (arm-to-tongue) were also measured.

CASE REPORT

History.—D. K., History No. 254438, a colored girl, aged 14 years, was admitted to the Medical Service of the New York Hospital January 6, 1940, with the chief complaint of blurring of vision of five months' duration.

Present Illness.—Three years prior to admission, the patient first noticed the onset of weakness and sweating. These attacks gradually became more frequent. They were not associated with fever. Approximately one year before admission the patient began to have dyspnea on climbing one flight of stairs, a preference for sleeping on two pillows, and moderate polydipsia and polyuria. Severe bitemporal headaches of relatively short duration and sudden onset of blurring of vision began in July, 1939. About this time sweating became more profuse. In September, 1939, the patient's mother observed puffiness of the eyelids and swelling of the feet, and the patient began to complain of transient, sudden coldness of the hands and feet. Approximately two weeks before admission, there was a short period of tinnitus. There was no history of convulsions, syncope, memory loss, or disorientation.

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†The surgical aspects of this case are to be published from the New York Hospital and Department of Surgery, Cornell University Medical College, New York, N. Y.

Physical Examination.—The patient did not appear acutely ill. The temperature (rectal) was 37.4° C. The pulse and respiratory rates were 132 and 20 per minute, respectively. The blood pressure (right arm) was 210/120. The skin over the feet, legs, and hands was reddish, dry, and thickened, and appeared smooth and atrophic. There was profuse sweating over the trunk. The muscular development was poor. Examination of the eye grounds showed widespread edema about the left disc, which was almost totally obscured, and diffuse scarring and a few small, fresh hemorrhages of the retina were observed. The right fundus showed recent hemorrhages in the nasal field and fresh "cotton patches" of exudate in the temporal field and about the disc. The latter was almost invisible. There were many small, streak hemorrhages along the vessels. The arterioles bilaterally were extremely spastic. The heart was markedly enlarged; a diffuse, heaving impulse extended 10 cm. to the left of the midsternal line in the fifth intercostal space. Pulsus alternans was present. The heart sounds were loud. A protodiastolic gallop was heard at the apex. A rough systolic murmur was heard over the pulmonic area and down the left border of the sternum. The aortic second sound was accentuated. The pulsations in the two dorsalis pedis arteries were difficult to feel. The right kidney was readily palpated but appeared to be normal in size.

Preoperative Laboratory Data.—The range in specific gravity of the urine was 1.012 to 1.030. The amount of albumin varied from none to 2 plus. Occasional erythrocytes and granular casts were seen in the sediment. The blood cholesterol was 289 mg./100 c.c. On two occasions the serum protein was 7.8 and 5.7 mg./100 c.c., respectively. On three occasions the urea nitrogen was 16, 12, and 8 Gm./100 c.c., respectively. The phenolsulphonphthalein test showed a total dye output of 72.5 per cent in two and one-half hours. The urea clearance was 92 and 81 per cent, respectively, on different occasions. The fasting blood sugar was 82 mg. per cent. One-half hour after the ingestion of 100 gm. of glucose it was 138 mg. per cent, one hour afterward, 194 mg. per cent; it was 156 mg. per cent at the end of two two hours, and 130 mg. per cent at the end of three hours. All of the urine specimens during this test were negative for sugar except the second, which showed 1+ sugar. The creatine tolerance test showed a retention of 34.8 per cent. The serum chlorides were 93.4 and 88.0 millimolar equivalents per liter. The serum potassium was 4.3 millimolar equivalents per liter. The serum sodium was 135 millimolar equivalents per liter. The prothrombin was 100 per cent of normal. The basal metabolic rate was +46 per cent, +43 per cent, and +48 per cent, respectively, on different days.

Course.—The ease with which the right kidney was palpated, the general clinical picture, and the fluctuations in blood pressure (150 to 250 mm. Hg, systolic, and 118 to 160 mm. Hg, diastolic) suggested the possibility of an adrenal tumor. In order to explore this possibility, urograms were made January 18, 1940. The kidneys showed normal function. The superior calyx in the upper pole of the right kidney was deviated laterally. In the region of the right adrenal gland a small, irregular, calcific area was seen. On January 27, 1940, perirenal insufflation of CO_2 into the right adrenal area was carried out. Roentgenograms showed a large, rounded shadow of increased density, approximately 6 cm. in diameter, in the region of the right adrenal. The calcification was seen to lie within this shadow. A diagnosis of right-sided adrenal tumor was made. Pneumoradiographic examination of the left kidney region showed that the left adrenal was normal in size, shape, and position. Studies of the peripheral blood flow, basal metabolic rate, pulse rate, blood pressure, and circulation time were made the morning of February 4, 1940. The patient was transferred to the Surgical Service February 7, 1940. Before removing the tumor, surgical exploration of the left adrenal region was carried out February 20, 1940, and revealed a normal adrenal gland on that side. The convalescence from this operation was uneventful. The patient continued to suffer from

headaches and sweating. On the evening of March 4, 1940, she experienced persistent cough, tachycardia, rapid respirations, and profuse sweating. There were moist râles over the lower halves of both lungs. The blood pressure was 250/150. These alarming signs rapidly subsided, and later in the day the blood pressure was 190/140, with only a few râles at the bases. The blood pressure the following morning was recorded as 170/120. It was our impression that the patient had suffered from a hypertensive crisis, with pulmonary edema. Because of this attack, rapid digitalization was undertaken at once, and the patient was given maintenance amounts of digitalis. On March 7, 1940, adrenalectomy was carried out on the right side, and an adrenal tumor, measuring $5\frac{1}{2} \times 4\frac{1}{2} \times 4$ cm. and weighing 63.5 grams, was removed. During the operation a small nick was made in the pleura, causing right-sided pneumothorax. This was promptly closed. A transfusion was started at the completion of the operation, and the patient was returned to the pavilion in excellent condition. The pathologic diagnosis of this tumor was pheochromocytoma of low-grade malignancy. Biologic assay showed adrenalin-like effects when one cubic centimeter of the filtered saline extract of a portion of the tumor was slowly injected intravenously into a twenty-three-pound dog.* For the first few postoperative days, there was respiratory distress associated with the pneumothorax. Aspiration of air and an oxygen tent afforded relief. Roentgenograms taken March 22, 1940, showed practically complete expansion of the right lung. Postoperative excretion urograms showed that the renal shadows were normal. The right kidney now appeared to be in its normal position. After the operation the patient was free of headache, weakness, dizziness, sweating, polydipsia, and polyuria. On March 25, 1940, postoperative measurements of the peripheral blood flow, basal metabolic rate, pulse rate, blood pressure, and circulation time were again made. During the last ten days of her hospital stay the patient gained six pounds in weight. The average blood pressure was 117/73, and the pulse rate ranged usually from 80 to 90 per minute during the postoperative period. The patient was discharged twenty-six days after operation in excellent general condition. At this time the operative wounds were well healed. The use of digitalis, 0.1 Gm. daily, was continued.

Postoperative Laboratory Data.—The range of the specific gravity of the urine was from 1.015 to 1.030. The albumin varied from negative to one plus. Occasional erythrocytes and a few leucocytes were observed in the sediment. The hemoglobin was 13.5 Gm. (92 per cent). The erythrocyte count was 4.9 million. The serum chlorides on two occasions were 560 and 600 mg. per cent. The serum calcium was 11.7 mg. per cent. The creatine tolerance test showed a retention of 83.7 per cent. The basal metabolic rate was -17 per cent. Before operation the electrocardiogram showed slight left axis deviation, probably as a result of the hypertension. The low amplitude of T_1, together with the fact that T_2 and T_3 were diphasic, indicated myocardial damage. After the administration of digitalis, T_1 became negative, T_2 changed form, and T_3 became upright. On June 15, 1941, three months after operation and one month after discontinuing digitalis, the left axis deviation had disappeared and the T waves had all become upright and had a normal contour. On the whole, the electrocardiogram had a normal configuration.

Course After Leaving Hospital.—Studies of peripheral blood flow, basal metabolic rate, pulse rate, and blood pressure were repeated May 3, 1940. Digitalis was discontinued at this time. Studies of the peripheral circulation were carried out November 9, 1940, and again on March 22, 1941. The patient has been observed at intervals since discharge from the hospital. She has been free of complaints. The blood pressure and pulse rate have been normal during each observation. She has

*We wish to thank Dr. Frank Glenn, of the Department of Surgery, for permission to use these data.

gained weight. There has been slight progressive improvement in eyesight, and objectively the fundi show some peripheral clearing. She has gradually returned to a normal amount of physical activity and resumed work at school.

METHODS

The method used by Stewart and Jack[4] and Stewart and Evans [5, 6] in earlier measurements of peripheral blood flow was employed. This method requires the accumulation of certain data, namely, measurements of skin temperature, for which the Hardy-Soderstrom improved radiometer was used,[7] and measurements of rectal temperature, oxygen consumption, height, and body weight. The order in which data were collected has already been described[5, 6] All observations were made with the patient in a basal metabolic state. Six sets of skin temperature readings from eleven areas of the body and of rectal temperature measurements were taken at twenty-minute intervals. From these recordings, five average periods of peripheral blood flow were calculated. The pulse rates and blood pressures were also recorded. The arm to-tongue circulation time (Decholin[8]) was measured after the last estimation of oxygen consumption. The same sequence of observations was followed in the postoperative as in the preoperative studies, and the same environmental temperature was used.[5, 6] Data were collected once before, and on four occasions after, operation.

RESULTS

Basal Metabolic Rate and Peripheral Blood Flow.—Before operation, when the basal metabolic rate was increased to +48 per cent, the peripheral blood flow was only 59 c.c./M²/min. After operation the basal metabolic rate fell to −17, −13, −16, and −13 per cent, respectively, yet there were increases in peripheral blood flow to 90, 94, 92, and 99 c.c./M²/min., respectively. There was, therefore, a marked relative *increase* in peripheral blood flow during the postoperative period, at a time when there was a *fall* in the basal metabolic rate to normal (Table I) (Fig. 1).

Skin Temperature.—Before operation the average skin temperature was low. After removal of the tumor the average skin temperature was approximately 1° to 1½° C. higher. The temperature of the hands and feet showed trends similar to average skin temperature in both the preoperative and postoperative phases. There was, however, no constant relationship between average skin temperature and the temperature of the extremities during a morning's observations (Table I) (Fig. 1).

Rectal Temperature.—At first, when the average skin temperature was decreased (32.45° C.), the rectal temperature was elevated (37.93° C.). After operation the rectal temperature was normal during each of the observations, at a time when the average skin temperature had risen to normal (Table I) (Fig. 1).

Pulse Rate.—Tachycardia was present before operation, but the rate fell to normal after removal of the tumor (Table I) (Fig. 1).

Blood Pressure.—The systolic and diastolic pressure was markedly elevated before operation and fell to normal after operation (Table I) (Fig. 1).

TABLE I

AVERAGE VALUES OF MEASUREMENTS ON D. K.

		BEFORE OPERATION	AFTER OPERATION			
			18 DAYS	2 MONTHS	8 MONTHS	1 YEAR
Digitalized		No	Yes	Yes	No	No
Basal Metabolic Rate	Per Cent	+48	-17	-13	-16	-13
Peripheral Blood Flow	C.c./M²/Min.	59	90	94	92	99
Circulation Time	Seconds	11.3	-	-	13.6	13.8
Blood Pressure	Mm. Hg	190/130	120/84	118/80	98/54	98/64
Pulse Rate	Per Min.	138	82	72	70	60
Average Skin Temp.	Degrees C.	32.45	33.60	34.23	34.20	34.08
Average Hand Temp.	Degrees C.	31.10	32.90	34.20	34.20	33.30
Average Foot Temp.	Degrees C.	26.80	27.50	33.20	28.60	29.50
Average Rectal Temp.	Degrees C.	37.93	36.93	37.26	37.27	37.03
Heart Area	Sq.Cm.	99.1	103.8	-	100.9	-

DISCUSSION

The objective measurements now being reported show that there was, relatively, a marked decrease in peripheral blood flow when patient D. K. was suffering from an adrenal pheochromocytoma, for the peripheral blood flow was only 59 c.c./M²/min. at a time when the basal metabolic rate was increased to +48 per cent. After operation, although the metabolic rate decreased to a normal level, there was an average increase of 60 per cent in the amount of blood allotted to the peripheral circulation (Table I) (Fig. 1). Stewart and Evans[3] showed that, at a similar environmental temperature, patients suffering from hyperthyroidism with basal metabolic rates comparable to the preoperative level of subject D. K. had a peripheral blood flow of approximately 225 c.c./M²/min. After operation, when these same subjects were within the normal metabolic range, the average peripheral blood flow was approximately 70 c.c./M²/min. Comparing these data for the two diseases, it is evident that subject D. K. had a marked reduction in peripheral blood flow at a time when the oxygen consumption might require it to be greater. Perfusion experiments, made with an extract of the tumor, showed that it contained an adrenalin-like substance. It is proper to assume, therefore, that it was this substance, elaborated by the tumor, which induced these circulatory phenomena in this patient. It is known that one of the actions of epinephrine is to decrease peripheral blood flow. After removal of the tumor the basal metabolic rate decreased and peripheral blood flow increased.

The elevated heat production attendant upon increased oxygen consumption usually brings about a high skin temperature.[5] In subject D. K., the average skin temperature before operation was low at a time when the basal metabolic rate was high. After operation it increased to normal. Vasoconstriction is one of the actions of epinephrine. Low skin temperature was to be anticipated before operation, therefore, because peripheral vasoconstriction and decreased peripheral blood flow were present during hyperadrenalemia. As a consequence, the skin

could not dissipate efficiently the increased amount of heat produced, and increased heat storage and a high rectal temperature resulted. At this point it may be of interest to speculate upon the mechanism of the attacks of profuse perspiration which occurred before operation. There is reason for the opinion that they were not initiated entirely by direct sympathetic stimulation of the sweat glands by adrenalin, for they occurred in attacks. If there was an increased amount of circulating adrenalin at the time of sweating, an additional elevation of blood pressure would be expected also. There were no unusual rises in blood pressure or hypertensive crisis during these attacks while the patient was under observation, except for the one instance mentioned in the case report. Another explanation which appears most applicable is that the heat regulating center, finding the internal temperature (rectal) too high, responded by calling for profuse perspiration intermittently in order to bring into action the cooling effect of evaporation.

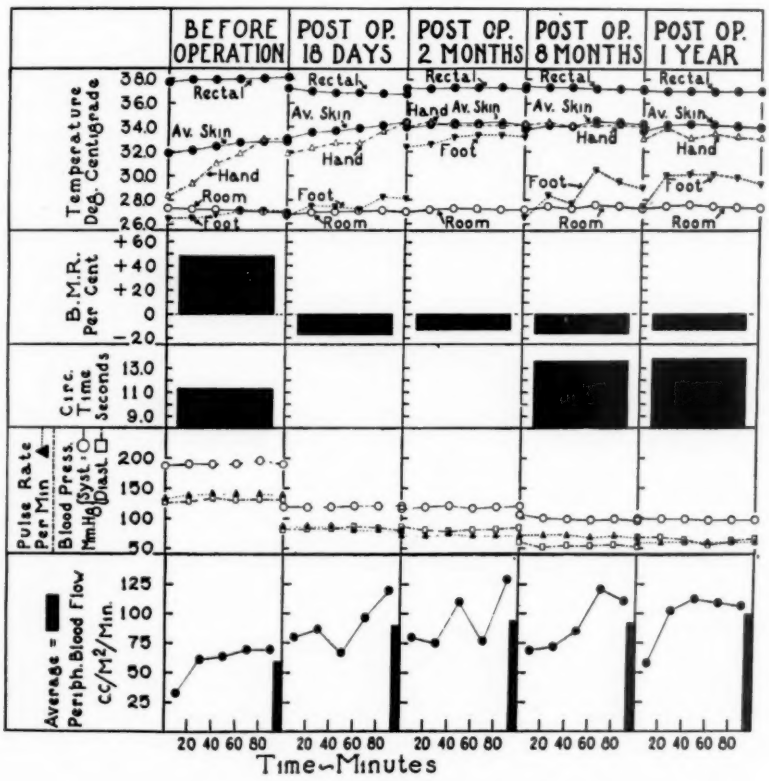

Fig. 1.

The temperature of the hands and feet showed trends similar to average skin temperature in both the preoperative and postoperative phases. There was no constant relationship between average skin temperature and the temperature of the extremities during a morning's observations.

Fatherree and Allen,[9] in observations on the vasoconstrictor effects of epinephrine on the digital arterioles, found a more prolonged action in the toes than in the fingers. Moreover, they were of the opinion that the vasoconstrictor action in normal persons may vary widely, giving rise to marked variability in the skin temperature of different digits, and in the same digit at different times in the same subject. To some extent, the results in this patient (Table I) (Fig. 1) parallel those obtained by Fatherree and Allen.[9] Hardy[10] found, in subjects who were receiving an infusion of epinephrine, a marked fall in the skin temperature and peripheral blood flow of the extremities at the same time that the average skin temperature and average peripheral blood flow were increased. Before operation in our case, not only the temperatures of the extremities, but also the average skin temperature and average peripheral blood flow of the whole body surface were decreased. These observations are not at variance with the work of Hardy, for it is well known that the pharmacologic action of smaller amounts of adrenalin will be primarily reflected in the extremities, whereas, with larger amounts, the effects are of a widespread nature.

The continuous tachycardia before excision of the pheochromocytoma was probably a response, in part, to sympathetic stimulation by adrenalin, and, in part, to the increased oxygen consumption. After operation the heart rate returned to normal.

The persistent elevation of blood pressure (average, 190/130) before operation was not the result of permanent changes in the vascular tree, because the pressure returned to normal after operation. Although the tumor from which this subject was suffering supplied the circulation constantly with increased amounts of adrenalin, it apparently was capable of flooding additional amounts into the circulation, because there occurred sudden rises in systolic pressure from the usual level of 190 mm. Hg to 260 mm. Hg, and in the diastolic from 130 mm. Hg to 150 mm. Hg.

The circulation time (arm-to-tongue) was shorter before operation (11.3 seconds) than after operation (13.6 seconds and 13.8 seconds). Patients with thyrotoxicosis, with preoperative basal metabolic rates comparable to this patient's (+48 per cent), had circulation times which were two to four seconds shorter.[5] The velocity of blood flow may have been less rapid in this subject before operation because of the resistance offered to blood flow by vasoconstriction.

SUMMARY

(1) Using a method which Stewart and Jack[4] and Stewart and Evans[5, 6] employed previously, measurements were made of the peripheral blood flow, and certain other data were collected, on a patient with an adrenal pheochromocytoma, before operation and at intervals for one year afterward.

(2) Before operation, at a time when the basal metabolic rate was high, there was a marked relative decrease in the peripheral blood flow in c.c./M^2/min. After operation the basal metabolic rate fell to normal, and an increase in peripheral blood flow occurred. The decreased peripheral blood flow before operation was attributed to hyperadrenalemia.

(3) The circulation time was shorter before operation than afterward.

(4) The low average skin temperature and the high rectal temperature before operation were interpreted as being brought about by decreased peripheral blood flow and vasoconstriction, with resulting inefficiency in heat loss and increased heat storage. As an explanation for the periods of marked sweating, these observations suggest that the organism increased heat loss by the cooling effect of evaporation. After operation the skin and rectal temperatures returned to normal.

(5) No definite relationship was observed between the temperature of the hands and feet and average skin temperature during any of the observations. On the other hand, all temperatures rose after operation.

(6) The blood pressure and pulse rate were markedly elevated at first and returned to normal after operation.

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TUBERCULOUS ENDOCARDITIS

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AT BELLEVUE HOSPITAL we have recently had occasion to observe a case of tuberculous endocarditis superimposed upon an unusual congenital defect of the aortic valve, associated with certain changes possibly rheumatic in origin.

CASE REPORT

A. R., a colored man, 17 years old, was admitted October 13, 1940, complaining of gradually increasing dyspnea over a period of one and one-half years. This had become more pronounced during the preceding three or four weeks.

The patient denied having any illness previous to two years before admission; however, examination of the outpatient records of Harlem Hospital revealed that in March, 1936, he had applied for treatment there because of a "cough and cold." At that time he admitted having frequent attacks of epistaxis and was found to have a mitral murmur. During 1937 and 1938, because of pains in the knees and in the joints of the hands, he attended the orthopedic clinic, where a diagnosis of arthritis was made in 1938. He was hospitalized and tonsillectomy was done. There was no history of headache, hemoptysis, cough, or disturbances referable to the genitourinary system.

One and one-half years before admission to Bellevue Hospital the patient noted shortness of breath on climbing two flights of stairs. The dyspnea increased slowly, and he began to notice palpitation of the heart on exertion. On one occasion, about a year prior to admission, he experienced pain in the epigastrium; this gradually subsided. Ten months before we saw him he had muscle and joint pains and was not thereafter allowed to take part in sports at school. For several weeks before admission he had been occasionally short of breath even while at rest. There was no history of edema of the ankles, hemoptysis, or precordial pain during this time, nor of chills and fever. At no time had he received digitalis. He thought he had lost some weight.

Physical examination revealed a well-developed, fairly well-nourished young Negro. He was dyspneic but not cyanotic. Apparently he was in no acute distress, sitting quietly in bed. His temperature was 102° F., the pulse rate was 129, the respiratory rate, 36, and the blood pressure, 140/80. The skin was smooth, warm, and moist, and the mucous membranes appeared to be slightly pale. The lungs were resonant throughout and no râles were heard. There was a marked precordial heave which moved from apex to base, together with a systolic thrill over the apex and in the second left intercostal space anteriorly. The point of maximum impulse was in the left fifth intercostal space in the midaxillary line, where, also, the left border of cardiac dullness was found. In the third left intercostal space the cardiac dullness extended eight centimeters from the midsternal line. At the apex, loud, low-pitched, prolonged diastolic and presystolic murmurs blended with a systolic murmur. It was difficult to distinguish the systolic murmur which was heard over the aortic area from that over the apex. The pulmonic second sound was loud and booming, and of greater intensity than the

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aortic second sound. No friction rub was heard in any part of the chest. Neither the liver nor the spleen was palpable. The extremities showed no clubbing or edema, and there was no enlargement of the lymph nodes.

Examination of the urine was negative; it was acid, and the specific gravity was 1.015. The hemoglobin was 14.5 grams, the erythrocyte count, 5.9 million, and the leucocyte count, 13,000. The blood smear appeared to be normal; there were 62 per cent polymorphonuclear leucocytes, 4 per cent transitional cells, 30 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophiles. The blood Wassermann reaction was negative, the nonprotein nitrogen was 43 mg. per cent, and the blood sugar was 83 mg. per cent. The estimated sedimentation rate was 0.1 mm. an hour.

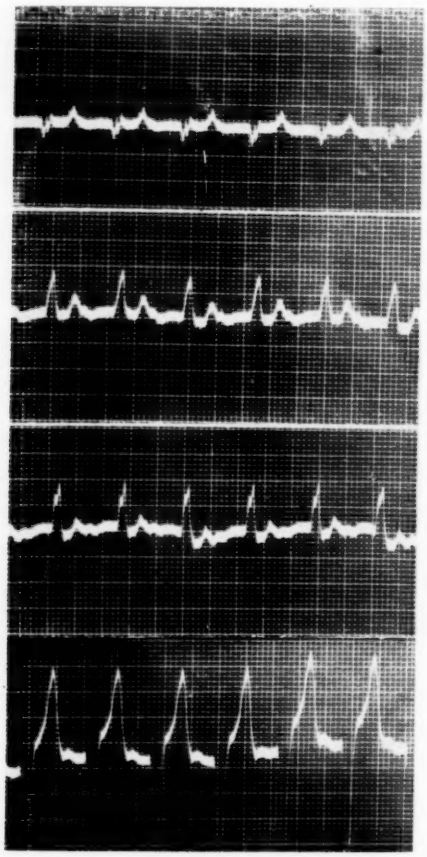

Fig. 1.

The electrocardiogram (Fig. 1) showed heart block, with a P-R interval of 0.28 sec., sinus tachycardia, and right axis deviation. In Lead I the Q wave was notched; in Lead II the R wave was slurred and the S-T segment negative; in Lead III the R wave was notched and the S-T segment negative; and in Lead IV the S-T segment was positive.

A roentgenogram of the chest (Fig. 2) showed an enlarged cardiac silhouette, centrally placed. The left cardiac border was elongated and bulging, and the right cardiac curve was accentuated. The pulmonic fields were not remarkable.

While in the hospital the patient at no time appeared to be acutely uncomfortable. On several occasions he was observed lying prone in bed, with his left side slightly elevated; when questioned about this he replied that breathing was easier when he assumed this position. His temperature ranged between 98.6° F. and 101° F., and his pulse rate, between 124 and 88. Digitalis, which was given to observe what effect it might have on the heart rate, not because of any signs of congestive failure, was of no apparent value. The patient's condition showed little change until the fifth day after admission when he had an "attack" which lasted about three minutes. Patients nearby called a nurse to see the patient, who was breathing very "heavily," with eyes rotated upward. He died a few moments thereafter.

The clinical diagnoses were active rheumatic heart disease with valvulitis, endocarditis, myocarditis, and pericarditis with effusion.

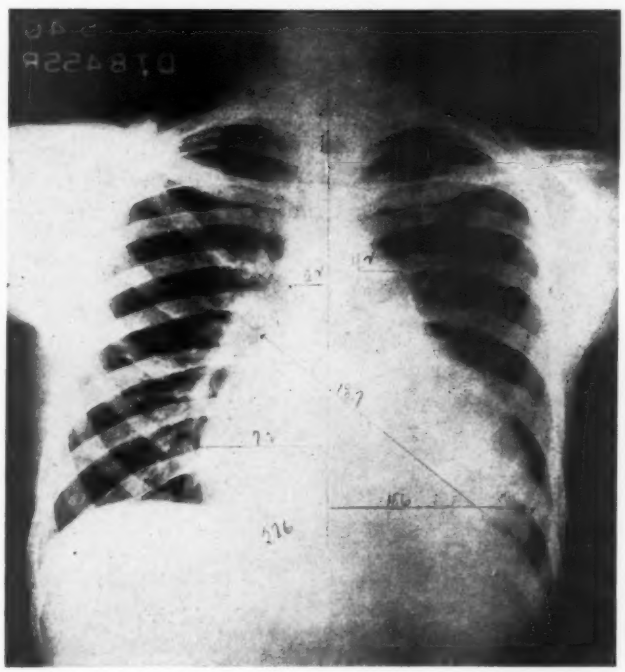

Fig. 2.

Necropsy (No. 28,473, Bellevue Hospital) was performed three hours after death. Seven hundred c.c. of serosanguinous material were found in each pleural cavity. The pleura was richly studded with gray-yellow, firm nodules about 2 mm. in diameter, some of which were surrounded by an area of hemorrhage. Similar nodules were uniformly distributed through both lungs. At the apex of the left lung there was a puckered scar. The precordial area occupied more than two-thirds of the anterior chest wall. Two hundred c.c. of exudate similar to that found in the pleural cavities were present in the pericardium. Even after its removal the heart appeared enlarged to the left, and over its anterior surface there was a granular, hemorrhagic exudate.

The heart weighed 690 grams. The left auricle was dilated. The endocardium of the left auricle was markedly thickened, and above the posterior mitral leaflet there was a conglomeration of minute gray nodules which measured about 1 cm. in diameter and 2 to 3 mm. in depth. They were firm and apparently covered by intact

endocardium. The mitral orifice was not stenotic, although both leaflets appeared fused and thickened, the posterior to a much greater extent than the anterior, so that it assumed a fusiform shape along the line of closure (Fig. 3). On section through this thickened tissue, yellowish cheesy material could be scraped from the cut surface. The chordae tendineae were slightly shortened, but not thickened or fused. The left ventricle was dilated. The aortic valve was the seat of an anomalous formation. Failure of the cusps to fuse with the ventricular endocardium for a distance of 5 cm. from their free edges produced aneurysmal dilatations which were distended with clotted blood (Fig. 4). There was no connection between these outward pouchings and the substance of the mitral valve. Immediately below their line of closure the cusps assumed a fibrous and nodular appearance. Yellowish plaques extended downward over the aortic surface of the mitral valve. The lumen of the left circumflex coronary artery, 4 cm. from its origin, was narrowed to the size of a pin point for a distance of 0.5 cm. by an endarterial process (Fig. 7). Beyond, the coronary artery showed moderate, patchy, fibrous thickening. The anterior descending ramus of the left coronary artery was involved by a similar process which, however, was less pronounced than that observed in the circumflex. The right side of the heart was apparently well preserved.

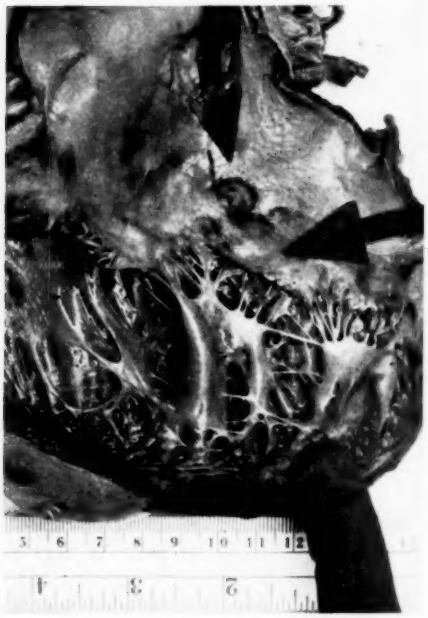

Fig. 3.

Fig. 4.

Fig. 3.—Arrows point to endocardial nodules in left auricle and swollen, deformed, posterior mitral cusp. Gloved finger near apex.

Fig. 4.—Arrows showing malformed cusp, with resulting aneurysmal dilatation. Also blood clot within sac. Note nodular, irregular surface of valve.

The aorta was smooth and elastic, and measured 7 cm. in diameter above the sinus of Valsalva, in contrast to 10 cm. at the ring.

There were 500 c.c. of clear, straw-colored fluid in the abdomen. The liver was enlarged and presented a nutmeg appearance. The spleen was about normal in size, firm, and showed numerous hyperplastic follicles, as did the mucosa of the terminal ileum and colon.

The anterior mediastinal, hilar, and paratracheal lymph nodes, as well as a few of the mesenteric nodes, were tremendously enlarged and discrete, and, on section, the cut surfaces were flecked with pin-point yellow dots which were occasionally confluent. In the confluent areas the consistency was soft and the substance was caseous. The solitary enlarged axillary node showed the same changes.

Post-mortem culture of the spleen and mitral valve yielded no growth.

Fig. 5.—Sections through posterior mitral leaflet showing (b) areas of caseation and (a) abscess composed of purulent exudate in which giant cells are seen.

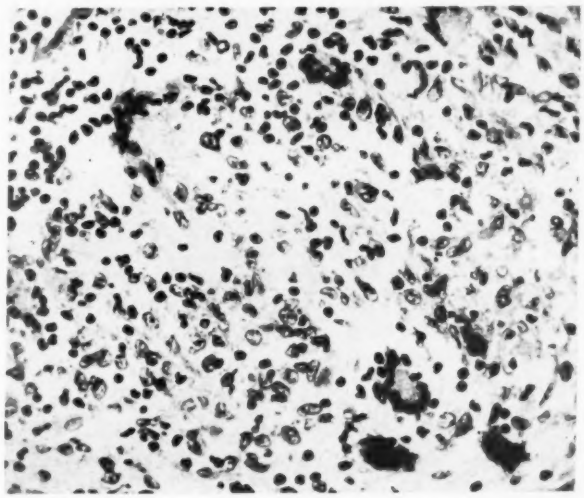

Fig. 6.—High power of area in posterior mitral leaflet showing giant cells, epithelioid cells, and a few small lymphocytes.

Microscopic examination of tissue removed from the left auricle showed that the endocardium became abruptly distended and fragmented over a mass of fibrin in which a few erythrocytes were enmeshed. This gave way to extremely vascular and edematous granulation tissue. An occasional vessel showed fibrosis of its walls, but thin-walled, apparently newly formed capillaries were predominant. Scattered diffusely through this tissue, but with a tendency toward segregation in nests, were small lymphocytes and polymorphonuclear leucocytes, together with great numbers

of eosinophiles. No Aschoff bodies or Langhans giant cells were observed. The underlying myocardium showed some congestion and a small degree of infiltration by leucocytes.

Sections through the posterior leaflet of the mitral valve showed tremendous thickening, with subendocardial hemorrhage. As in the case of the left auricle, fibrosis of vessels could be seen and was even more prominent, and the same type of granulation tissue was present. In the posterior mitral leaflet there was a widespread destructive lesion, in the center of which was a small abscess. In addition, large areas of caseation necrosis were present. In them, polymorphonuclear neutrophiles were present in large numbers, together with Langhans giant cells, epithelioid cells, and lymphocytes (Figs. 3, 5, 6).

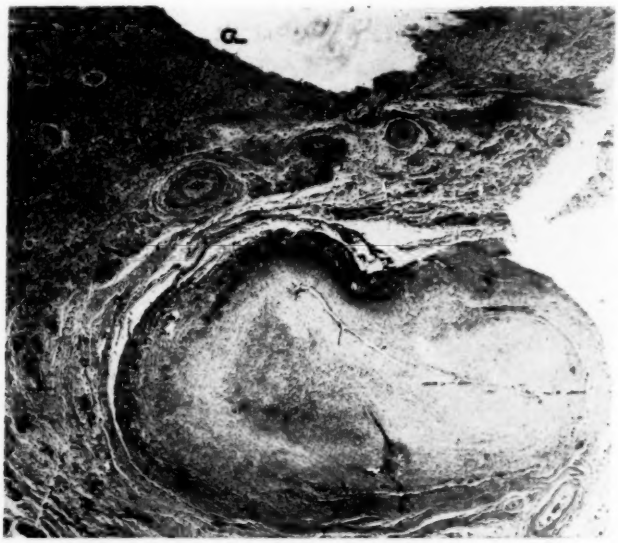

Fig. 7.—Section through the left circumflex coronary artery showing slit-like lumen due to extensive fibrosis and proliferation of intima. Note also extensive endarteritic changes in small vessels. At upper edge (a) is lowermost border of aneurysmal sac of left aortic cusp filled with caseous material.

Other sections from the posterior cusp presented a picture practically identical with the foregoing. Sections of the anterior leaflet, taken at a distance from the lesion, revealed no evidence of recent or previous damage.

Sections from the posterior cusp of the aortic valve, including part of the contents of the aneurysmal sac, revealed, perhaps, the most highly destructive lesion of all. The margin appeared to be well-preserved, but at a short distance beneath the margin the thickened fibrotic cusp was replaced by cellular and partially necrotic tissue which, in places, appeared hyalinized. An occasional giant cell of the Langhans type was found. Here, again, large numbers of eosinophiles were present. Masses of caseous material were found both replacing and attached to the cusp, as well as enmeshed in the organizing thrombus.

Sections through the left circumflex coronary artery showed, in the adjacent epicardium, dense collections of lymphocytes. Congested capillaries were numerous. The coronary artery and all of its visible branches were the seat of obliterative endarterial fibrosis which reduced their lumina to mere slits and, in some instances, to complete extinction. The muscular walls appeared hyalinized, and the intima was fibrosed. The endothelium was intact. In the same sections, which included remnants of an aortic cusp, caseation necrosis, epithelioid cells, and an occasional Langhans giant cell were evident (Fig. 7).

Sections through the interventricular septum revealed marked thickening and hyalinization, and, near the myocardium, congested capillaries and numerous small, fibrotic vessels. This scarring extended deep into the myocardium and replaced it. Diffuse myocardial fibrosis, often perivascular and accompanied by endarterial changes, was seen throughout the sections.

The microscopic changes in sections of other areas of the myocardium varied with the location. Those taken close to the base of the left ventricle showed the most marked changes, which diminished halfway through the myocardial wall. The overlying epicardium exhibited discrete collections of lymphocytes, epithelioid cells, and congested capillaries. The smaller vessels showed endarterial fibrotic changes. Similar collections of cells near a coronary vein and nerve showed, in addition, Langhans giant cells, and were obvious attempts at tubercle formation. In the myocardium, discrete collections of small round cells, resembling those in the epicardium, and perivascular fibrosis were apparent. In the wall of a myocardial vein was a raised plaque, composed of lymphocytes and epithelioid cells, that had disrupted the intima.

Sections from the apex of the left ventricle and from the right ventricle showed small areas of myocardial degeneration and fibrosis.

In numerous sections from the lungs there were small, uniformly distributed tubercles with caseous centers and a few Langhans giant cells.

The spleen showed chronic passive congestion and hyperplasia, both of the follicular cells and small lymphocytes in the Malpighian bodies. No tubercle formation was observed in the spleen.

The liver, kidneys, and adrenals were the seat of chronic passive congestion.

The intestinal sections showed lymphoid hyperplasia of the solitary follicles, but no tubercle formation.

In the lymph nodes of the anterior mediastinum and the mesentery, and in an enlarged axillary node, widespread tuberculous caseation had replaced the normal architecture. In some areas the reaction was one of proliferation, but exudation and caseation were predominant.

Sections from the lymph nodes and heart, stained by the method of Ziehl-Neelsen, revealed a few acid-fast bacilli which were morphologically indistinguishable from tubercle bacilli. In the heart valves these organisms lay in the substance of the valve. In all of the sections thus stained, even in the caseous lymph nodes, acid-fast bacilli were scarce and were found only after diligent search.

Gram-Weigert stains of the heart valves failed to show other bacteria. Sections stained by the older method of Levaditi were negative for spirochetes.

COMMENT

The history, physical examination, and laboratory data were compatible with a diagnosis of rheumatic heart disease. There was nothing to suggest an unusual clinical entity.

We feel that the case here recorded fulfills the requirements for the gross and histologic diagnosis of caseous tuberculosis of the heart valves and endocardium. In addition, it affords some support to the theory of allergic sensitization, advanced by Davie, because of the large numbers of eosinophiles in the valve lesions.

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Abstracts and Reviews

Selected Abstracts

Blair, H. A., Wedd, A. M., and Hardwicke, H. M.: The Normal Pneumocardiogram. Am. J. Physiol. **136:** 523, 1942.

Pneumograms of the chest, the abdomen, the neck, and the thigh taken during suspended breathing are related to the electrocardiogram and to the venous and arterial pulses. Ejection during systole of arterial blood from the chest creates there a fall in pressure which causes collapse of the chest wall, a probable rise of the diaphragm, and aspiration of venous blood from the neck and abdomen. The effect on the abdomen is such that it also collapses. The volumes of the neck and thigh increase to compensate for the decreased volume of the trunk. During diastole, the chest and abdomen expand because venous return exceeds arterial outflow. When decrease of the volume of the chest is recorded in the same direction as increase of pressure in the artery, the pneumocardiogram of the chest is similar in form to a record of the carotid pulse. The pneumogram usually indicates the beginning of isometric contraction of the ventricles, the beginning of ejection from the chest, the beginning and end of isometric relaxation, auricular filling, and sometimes auricular contraction. It yields, in general, more information than the pulse, yet it is much easier to record. It is concluded that the low pressure of the neck veins during ventricular systole is due to the aspirating action of arterial ejection. Aspiration of venous blood is probably an important factor in promoting venous return. The rise of the venous v wave is thought to be due to ventricular relaxation. The part played by relaxation of the ventricles in producing characteristic waves in the pneumograms of the chest and abdomen and the notch in the arterial pulse is stressed. The relation of the Q wave of the electrocardiogram to the beginning of ventricular contraction and of the T wave and the second sound to ventricular relaxation is determined for a group of normal subjects. Electrical and mechanical systole are seen usually to begin very close together.

AUTHORS.

Mayerson, H. S.: The Influence of Posture on Blood Flow in the Dog. Am. J. Physiol. **136:** 381, 1942.

Tilting of anesthetized dogs to the upright (75°) position, feet down, resulted in a consistent and marked decrease in the rate of blood flow in the femoral vein and artery and a less pronounced fall in the carotid artery and jugular vein. Changes in renal flow were less consistently observed, but in the majority of experiments were in the same direction.

L. W. ROTH.

Lebowich, R. J., Opps, F. A., and Procita, L.: Simultaneous Soap-Wax Dehydration and Infiltration of the Human Heart: A Method for Permanent Preservation. Arch. Path. **33:** 696, 1942.

A rapid and simple technique is described for the dry preservation of the human heart without sacrifice of color through infiltration by a warm liquid soap-wax solution in a specially constructed vacuum apparatus.

It possesses the advantages of economy, through the elimination of costly museum jars and preserving fluids, and of permanence of preservation.

Tissue sections can be prepared from the finished specimen that are superior to those obtained with the paraffin infiltration techniques.

AUTHORS.

Bernstein, P., and Mann, H.: A Clinical Evaluation of Fetal Electrocardiography: A Study of 100 Cases by a New Technique and an Improved Instrument. Am. J. Obst. & Gynec. **43**: 21, 1942.

In summarizing the results described, the following conclusions may be stated:

A fair sample, consisting of the first 100 consecutive full-term pregnancies, terminated by normal labors, was studied. In this sample, an almost equal number of parous and nulliparous, white, and Negro women of all ages, is found. Vertex presentations singularly occurred in all but four cases. The number of male and female infants was almost similar.

Constancy of method, technique, and personal error was maintained since all tests were performed by one of the authors.

A cursory outline of historical data is briefly mentioned along with the technical difficulties previously experienced.

A new technique, describing variations in position of electrodes as well as the small convenient portable electrocardiographic instrument, is described. Several complications, inherent physical disturbances, which may alter or obstruct clear recordings, are pointed out. Generally, larger, more obese women yielded inferior electrocardiograms.

Only two patients of the entire group failed to exhibit satisfactory fetal curves at some time during pregnancy.

Ninety-eight out of 100 patients showed one or more satisfactory curves. The maximum number of records of any single patient was four.

Seventy-five per cent of 153 tests performed on 100 patients showed clear-cut curves. Those which were not clear were considered negative.

No positive electrocardiograms were obtainable earlier than the fourth lunar month. In this month, 33 per cent of nine readings were positive. In the third month no records were successful.

The individual monthly percentages of positive results ranged from 53.8 to 96.5 per cent. The average of all monthly percentages, from the fourth to tenth lunar months, inclusive, was 77.86 per cent.

In the last two months combined, it is significant that a total of 48 readings yielded 96 per cent positive readings.

The fetal heart rate is no index as to the fetal sex, since both sexes averaged 148.7 beats per minute. No correlation between the rate and the color of the fetus is found.

There was a tendency for a gradual but definite decline in the fetal heart rate to the eighth lunar month; from then on to delivery, there was a slight rise. The duration of the pregnancy in any instance cannot be estimated by the rate.

Fetal and maternal rates cannot be correlated; a change in one did not necessarily accompany a corresponding alteration in the other.

The electrocardiogram furnished a reliable diagnostic test in pseudocyesis of the menopause, suspected pregnancy due to amenorrhea with a large fibroid and huge ovarian cyst, as well as a missed abortion.

Electrocardiograms successfully indicated fetal viability in four instances in which fetal movements were not felt and in which the fetal heart was inaudible.

The presence of multiple pregnancies was accurately diagnosed in one case.

A marked increase in two cardiograms taken thirty-five days apart within six weeks of labor, proved to be due to an unsuspected anomaly, gastroschisis fetalis with hydramnios.

In another teratologic birth, thoracoabdominoschisis with anencephalus, in which the apex of the fetal heart was drawn cephalad in a 180° version by congenital adhesions, the T waves were inverted. This suggests the possibility of determining a breech presentation.

Generally, fetal hearts show sinus arrhythmias and occasionally show extrasystoles and varying degrees of partial block.

Intrauterine anomalies usually produce peculiar electrocardiograms in which the rate shows a marked rapidity.

Before cesarean section is performed in instances of doubtful viability, an electrocardiogram is indicated.

Electrocardiography with the above technique and new instrument was found by us to be a practicable procedure in all pregnancies between the fourth and tenth lunar months.

AUTHORS.

Garvin, C. F.: Age, Sex and Race Relationships of Auricular Fibrillation. Am. J. M. Sc. **203**: 788, 1942.

The average age of death of 207 patients with hypertensive heart disease and a normal cardiac mechanism was 52.8 years; of 57 patients with hypertensive heart disease and auricular fibrillation, 62.3 years. Patients with coronary heart disease and a normal cardiac mechanism (142) averaged 59.8 at death; 35 patients with coronary heart disease and auricular fibrillation averaged 69.1 years. Fifty-eight patients with rheumatic heart disease and a normal mechanism died at an average age of 38.4 years; 61 who had rheumatic heart disease and auricular fibrillation died at an average age of 44.2 years. All these differences seem to be statistically significant. It would appear that the average age at death of cardiac patients with auricular fibrillation is greater than the average age of cardiac patients with a normal cardiac mechanism.

No association between auricular fibrillation and sex or race was demonstrable.

AUTHORS.

Baylin, G. J.: Patent Interauricular Septum Associated With Mitral Stenosis: Lutembacher's Syndrome. Radiology **38**: 1, 1942.

Two cases of patent interauricular septum with mitral stenosis are presented.

The syndrome presents a characteristic roentgenographic picture, in which enlargement of the pulmonary conus and the hilar shadows predominate, along with the right auricular hypertrophy.

AUTHOR.

Stalker, H.: Coarctation of the Aorta: A Case With Right Axis Deviation of the Electrocardiogram and Auricular Fibrillation With Some Statistics. J. Michigan M. Soc. **41**: 40, 1942.

A case is presented of adult type of coarctation of the aorta, not associated with any other congenital lesion, in a male of fifty years of age who showed right axis deviation in his electrocardiogram and a markedly dilated and hypertrophied right heart. The patient had shown a left ventricular failure as evidenced by dyspnea and orthopnea since he was first seen. This would be the primary strain to be expected with coarctation of the aorta and associated arterial hypertension.

It is concluded that his right ventricular failure with right axis deviation and hypertrophied right heart must have been the natural sequence from the left ventricular failure.

AUTHOR.

Stewart, W. H., Breimer, C. W., and Maier, H. C.: Cineroentgenographic Diagnosis of Congenital and Acquired Heart Disease. Am. J. Roentgenol. **46**: 636, 1941.

In addition to the elucidation of the nature of some congenital cardiac lesions, and the visualization of the cardiac chambers, various abnormalities of the great vessels have been demonstrated. Compression of the large venous trunks may be visualized. The size and course of the pulmonary arteries can be clearly shown. Mediastinal tumors and vascular structures may be differentiated. Cineroentgenography may be able to clarify our knowledge of the living anatomy and physiology of the central portion of the circulatory system. This method can be employed for educational purposes.

While up to the present it has not been possible to visualize a patent ductus arteriosus, the authors have detected certain abnormalities of the greater blood vessels as well as cardiac septal defects which would contraindicate surgical relief in a "patent ductus" detected clinically.

AUTHORS.

Rossien, A. X.: Complete Heterotaxia Associated With Obstructive Jaundice. Canad. M. A. J. **46**: 572, 1942.

The clinical significance of situs transversus viscerum totalis is related chiefly to differential diagnosis, since it does not interfere with the life span or physical status of the individual.

None of the theories as to the cause of this anomaly seems to merit being accepted as conclusive. The author believes that more frequent x-ray studies will show that sex plays no part in visceral mirror transposition.

A case complicated by obstructive jaundice is presented.

AUTHOR.

Lowry, O. H., Gilligan, D. R., and Hastings, A. B.: Histochemical Changes in the Myocardium of Dogs Following Experimental Temporary Coronary Occlusion. Am. J. Physiol. **136**: 474, 1942.

Dog hearts were examined chemically at various times following the termination of temporary occlusions of a major coronary artery. Characteristic increases in the water, chloride, and sodium content of the myocardium were observed. In general, there was little change in the potassium concentration.

These changes have been interpreted histochemically as denoting an increase in the proportion of extracellular fluid without demonstrable change in the muscle fibers themselves.

Occlusions lasting twenty minutes or less produced an increase in extracellular fluid which persisted four hours but not twenty-four hours. Occlusions lasting forty-five minutes produced a relative increase in the amount of extracellular tissue present both four hours and two weeks after the occlusion.

AUTHORS.

Wood, E. H., and Moe, G. K.: Electrolyte and Water Content of the Ventricular Musculature of the Heart-lung Preparation With Special Reference to the Effects of Cardiac Glycosides. Am. J. Physiol. **136**: 515, 1942.

Studies of the electrolyte and water content of the heart-lung ventricle are reported.

The ventricles of the untreated (failing) heart-lung heart have: an increased water content; an increase in the wet and dry weight sodium and chloride concentrations; a decrease in the wet and dry weight potassium concentration. Cor-

rection for edema and calculation of the "extracellular water" on the basis of chloride analyses indicate that: the intracellular water and electrolyte content of the untreated heart-lung ventricles is not significantly different from normal ventricles; the average edema content is 17.5 grams per cent of the final ventricular weight and is extracellular in position; the increase of sodium and chloride content of these hearts can be accounted for on the basis of the extracellular edema formation.

The ventricles of heart-lung preparations which received therapeutic doses of a digitalis glycoside have: an increased water content which is comparable to the control heart-lung ventricles; an apparent decrease in potassium content which is larger than that found in the control heart-lung and does not appear to be accountable for on the basis of an increased edema content alone.

The ventricles of heart-lung preparations which received toxic doses of a digitalis glycoside show significant changes in their intracellular electrolyte compositions. The intracellular potassium content is decreased apparently in exchange for sodium since there is approximately a chemical equivalent increase in intracellular sodium content. The doses of cardiac glycosides used in these experiments did not significantly affect the water gain or edema formation which occurs in heart-lung ventricles.

The unphysiological factor or factors which are responsible for cardiac edema formation in the heart-lung preparation must exert their chief effect on the capillary membrane, since the electrolyte concentration gradients across the muscle cell membrane and the intracellular water content of untreated heart-lung hearts are apparently normally maintained.

AUTHORS.

Saphir, O., and Wile, S. A.: Myocarditis in Poliomyelitis. Am. J. M. Sc. 203: 781, 1942.

Seven patients with poliomyelitis are reported, six of whom showed evidence at autopsy of varying degrees of myocarditis. Clinically, myocarditis could have been suspected in three patients because of a sudden "turn for the worse" without apparent cause, coincident with a rise in pulse rate and cyanosis. The myocarditis was characterized histologically by foci of perivascular infiltrations of lymphocytes and neutrophils. Foci of lymphocytes were also seen just beneath the endocardium. Though the number of inflammatory cells was never very large in any one area, they were present in many blocks cut from different parts of the different parts of the myocardium. The relation of the myocarditis to the bronchopneumonia which was present in four of the seven patients is discussed. The high incidence of myocarditis in this series warrants the consideration of supportive measures. The sudden death of three of these patients may be attributed to the myocarditis.

AUTHORS.

Lisa, J. R., Solomon, C., and Eckstein, D.: Persistent Tachycardia and Pulse-Temperature Disproportion: Relation to Acute Myocardial Lesions. Am. J. M. Sc. 203: 801, 1942.

In cases of persistent tachycardia and disproportion between the pulse rate and temperature level the acute myocardial lesions were studied. In 100 cases presenting the phenomenon, acute lesions were present in eighty, a chronic granulomatous lesion in one. In ninety-eight cases in which the phenomenon was absent, acute lesions were present in nineteen, a chronic granulomatous lesion in one and amyloidosis in one. The relation between the pulse and the temperature appears to offer a simple and valuable index to the presence or absence of acute myocardial damage in a high per cent of cases.

AUTHORS.

Raab, W.: Abnormal Suprarenal Discharges in Angina Pectoris and Their Control by X-ray Therapy. J. Clin. Endocrinol. **1**: 977, 1941.

Adreno-cortical (AC) compounds, which consist of adrenalin combined with cortical sterols were quantitatively determined in the blood of individuals with and without angina pectoris by chemical method.

In angina patients the blood AC level, although generally normal at rest, showed abnormally intense, sharp elevations after physical exercise. These elevations persisted for several minutes. The AC compounds which were discharged into the blood stream during physical exercise were particularly rich in adrenalin.

Therapeutic roentgen irradiation of the suprarenal glands, if successful, resulted in disappearance of the abrupt AC discharges on effort, coinciding with complete or almost complete disappearance of the subjective anginal symptoms for periods of several months.

The significance of these observations is discussed from the point of view of the theory that angina upon effort is caused by the specific anoxiating effect of sudden suprarenal discharges upon the heart muscle whose oxygen supply is inadequate due to sclerosis of the coronary arteries and their inability to dilate adequately.

AUTHOR.

Smith, C., Sauls, H. C., and Stone, C. F.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans: A Survey of the Present Status of the Previously Reported Cures and a Clinical Study of Fifteen Treated Cases, Including Another Cure. J. A. M. A. **119**: 478, 1942.

There has been a gradually decreasing mortality rate in subacute bacterial endocarditis since the advent of the sulfonamides.

The literature has been searched for authentic instances of cure of subacute bacterial endocarditis due to Streptococcus viridans and 35 reports were found. The authors of these reports were written to and follow-up notes to date have been obtained.

The clinical records of 15 patients treated by several physicians at the Piedmont Hospital and Emory University Hospital which have been tabulated show that there were 2 patients who recovered in this group.

Various therapeutic procedures have been used in combination with the sulfonamides including heparin, neoarsphenamine, hyperpyrexia by diathermy, and hyperthermia with typhoid-paratyphoid vaccine. The latter is most recent and in a small series of cases has afforded the best recovery rate. Because of increased tolerance without decreased efficiency, sulfadiazine with intravenous typhoid is probably the method of choice at the present time and should receive extensive clinical trial.

Clinical trial on larger groups of patients with the combined uses of sulfadiazine and the intravenous use of typhoid-paratyphoid vaccine should be carried out. This method has so far offered the best recovery rate, but the number of patients treated in this manner is too small to justify final conclusion at this time.

Surgical ligation must be considered for those patients having patent ductus arteriosus associated with subacute bacterial endocarditis.

AUTHORS.

Spink, W. W., Titrud, L. A., and Kabler, P.: A Case of Brucella Endocarditis With Clinical, Bacteriologic, and Pathologic Findings. Am. J. M. Sc. **203**: 797, 1942.

The clinical, pathologic, and bacteriologic data are detailed for a patient with brucella endocarditis.

The patient received a total of 31 Gm. of sulfathiazole and 236 Gm. of sulfanilamide. This therapy had no effect upon the bacteremia, and only temporary clinical improvement was observed.

AUTHORS.

Yampolsky, J., and Powel, C. C.: Syphilitic Aortitis of Congenital Origin in Young Children. Am. J. Dis. Child. **63**: 371, 1942.

The case of a colored patient 9 years of age with both a maternal and a birth history of syphilis is presented.

Pathologically the aortitis has been diagnosed as of syphilitic origin, and the case must be classified as one of syphilitic aortitis due to congenital syphilis.

AUTHORS.

Wile, U. J.: The Principles Underlying the Treatment of Cardiovascular Syphilis. Ann. Int. Med. **15**: 817, 1941.

The fundamental principles governing the treatment of cardiovascular syphilis embrace the careful appraisal of each case with regard to the therapeutic response which might reasonably be expected from the type of lesion present.

Cases in which failure is present should receive treatment no different from that given heart failure from other causes.

Cases most favorably influenced by anti-syphilitic treatment are those in which physical signs exist without symptoms, and in which there has been little or no previous anti-syphilitic therapy.

Asymptomatic cases, in which treatment directed toward syphilis has been energetic in earlier years, may often be singled out as cases which need no treatment whatever.

The beneficial effects of anti-syphilitic treatment upon cardiovascular syphilis are in a measure the result of the treatment with the drugs of choice upon subclinical syphilitic lesions in parts of the body remote from the heart itself.

Intensive treatment, such as is given in early syphilis, is seldom indicated in the late cardiovascular sequelae. Although beneficial results may be noticed with conservative arsphenamine therapy, the heavy metals, generally speaking, are considered safer and more productive of equally satisfactory therapeutic response.

AUTHOR.

Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema. Arch. Int. Med. **69**: 808, 1942.

Using a method which Stewart and Jack and Stewart and Evans have employed in earlier studies, measurements were made of peripheral blood flow in 6 patients suffering from myxedema when they were first seen before treatment and again on several occasions during the course of thyroid therapy. In addition, certain other measurements of the circulation were recorded. The results are summarized as follows:

In persons in a myxedematous state when the basal metabolic rate was low, the peripheral blood flow in cubic centimeters per square meter was decreased. With an increase in basal metabolic rate toward a normal level during the administration of thyroid, a progressive increase in peripheral blood flow occurred, so that a linear relation was maintained. These changes were opposite in direction to those observed in persons with thyrotoxicosis and confirm the relation between peripheral blood flow and basal metabolic in these two diseases.

The cardiac output is decreased in patients with myxedema. How the organs share this decrease is not known, but it is now shown that the amount of blood allotted to the periphery is decreased.

The circulation time treatment was prolonged. During treatment progressive decreases took place. Shortening of circulation time roughly ran parallel to an increase in basal metabolic rate and in peripheral blood flow.

The changes in pulse rate and pulse pressure followed roughly the increases in basal metabolic rate and peripheral blood flow.

For the most part, change in the average skin temperature followed the changes in basal metabolic rate and in peripheral blood flow.

No direct relation was observed between average skin temperature and the temperature of the hands and the feet.

No constant or significant changes in rectal temperature were observed during the several periods of study of each subject.

Conservation of heat has been suggested as an explanation for the decrease in peripheral blood flow in untreated patients suffering from myxedema.

AUTHORS.

Greene, A. M., and Hurxthal, L. M.: A Postoperative Follow-Up Study of Four Hundred and Sixty-Nine Thyrocardiac Patients. New England J. Med. 225: 811, 1941.

Four hundred and sixty-nine thyrocardiac cases in which operation was performed from 1922 to 1937 have been followed. In the first group of 303 patients, operated on between 1922 and 1932, 164, or 54.1 per cent, are living; 122 have normal heart rhythm, and 42 continue to have auricular fibrillation. Of the second group of 166 operated cases, 128 patients are still living, 98 of whom have normal heart rhythm.

The case mortality was 4.5 per cent, and the operative mortality was slightly less than 3.0 per cent.

The incidence of recurrent hyperthyroidism in the first group followed from six to sixteen years was over 10 per cent, which shows that the incidence increases the longer the period after operation.

Although these patients are restored to normal activity for the most part, their expectancy of life based on the present follow-up falls considerably short of the predicted expectancy.

AUTHORS.

Werle, J. M., Cosby, R. S., and Wiggers, C. J.: Observations on Hemorrhagic Hypotension and Hemorrhagic Shock. Am. J. Physiol. 136: 401, 1942.

By the expedient of regulated hemorrhages, dogs anesthetized with sodium barbital, amytal, or chloraslosane were kept in a state of severe hypotension for varying intervals, after which all the withdrawn blood (heparinized) was reinjected. Central arterial, central venous, and intrathoracic pressure changes were recorded throughout the experiments.

A continuing state of posthemorrhagic hypotension is not necessarily equivalent to shock, for in many animals (a) arterial pressures and pulses were restored to normal for many hours by reinfusion of the withdrawn blood even when such animals were on the verge of cardiac or respiratory failure, and (b) the viscera showed no pathological changes at autopsy.

If, however, both the intensity and duration of the posthemorrhagic hypotension were great enough, hemorrhagic shock developed for (a) the condition was only temporarily benefited by generous infusion of blood, and (b) the duodenal and jejunal mucosa was generally edematous, congested, and bleeding with presence of excessive fluid and blood in the lumen. Other organs showed no consistent pathological changes.

While the elusive "resistance factor" interferes with attempts to standardize the procedure for experimental purposes, our results suggest that the greatest hope

lies in creation of a preliminary period of moderate hypotension (ca. 50 mm.) followed by a shorter period of extreme hypotension (ca. 30 mm.). Using such a scheme, the minimum effective durations for these respective stages were found to be less than 90 and 45 minutes and more than 60 and 30 minutes in our trials.

We have discovered no new dynamic criteria which enables us to determine whether a period of posthemorrhagic hypotension will be followed by failure or recovery on reinfusion. Indeed, hemorrhage equal to 3 to 4 per cent body weight can produce all the changes in arterial pressure pulses seen in most severe shock due to other causes. Irreversibility after substantial infusion, admittedly unsatisfactory as a practical guide, is unfortunately the only reliable one at present.

Circulatory failure following reinfusion of all withdrawn blood developed despite an adequate blood volume and regardless of hemodilution or hemoconcentration. Augmented hemoconcentration induced by plasmapheresis had no discoverable accelerating action. The factor which precipitates the irreversible state of hemorrhagic shock resides in the cardiovascular system. Reduction of effective venous pressure did not account for the failure of arterial pressures in the majority of our animals. Since, in the majority, effective venous pressures were at or above normal levels during the postinfusion decline of arterial pressures, the deterioration of arterial pulses must be due to impairment of the heart, changes in the aorta and its elastic branches, and/or in the resistance at the periphery of the arterial tree.

The supervention of cardiac alternans during early periods of posthemorrhagic hypotension, the later tendency toward progressive slowing, the poor response to rapid infusions and the terminal rise of venous pressures suggest operation of a cardiac precipitating factor in some of our animals.

AUTHORS.

Foà, P. P., Woods, W. W., Peet, M. M., and Foà, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate, and Tubular Excretory Mass in Arterial Hypertension. Arch. Int. Med. 69: 822, 1942.

Effective renal blood flow, filtration rate, and renal tubular excretory mass have been determined for 20 patients with hypertension and for 7 nonhypertensive subjects.

The results indicate that arterial hypertension in man is accompanied by reduced renal blood flow, owing to increased resistance of the efferent glomerular vessels. However, they do not prove whether ischemia is a causal factor in hypertension or is simply one aspect of the systemic vascular disease. The relation between the function of the renal vessels and other clinical and morphologic observations is discussed. The latter include data on blood pressure, the condition of the eyegrounds, urine concentration, urea clearance, nonprotein nitrogen content of the blood and ratio of the wall to the lumen of the arterioles of intercostal tissue obtained for biopsy.

The patients are being studied approximately two weeks and six months after supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. The results of postoperative study will be reported in the future.

AUTHORS.

Kahn, J. R., and Laipply, T. C.: Frequency of Bilateral Renal Disease in Persistent Hypertension. Am. J. M. Sc. 203: 807, 1942.

From this study it is obvious that in nearly all cases of persistent hypertension with vascular disease the renal disease is bilateral. The renal involvement may be much more marked in one kidney than the other and can be so extreme as to produce a functionless or almost functionless organ. All known clinical tests of excretory function may fail to detect renal vascular disease. The weight and size of the kidney are not directly proportional to the degree or duration of the hypertension.

AUTHORS.

McLennan, C. E., McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm and Its Relation to Capillary Blood Pressure and Venous Pressure. J. Clin. Investigation **21**: 319, 1942.

The pressure plethysmograph was used to determine the effect of graded external pressure on the vascular volume of the forearm, for the purpose of determining the usefulness of this procedure in estimating the blood pressure in the minute vessels collectively.

With external pressure ranging from 0 to 90 mm. Hg, pressure-volume curves were determined in 20 normal subjects (a) by suddenly arresting the circulation to the forearm and measuring decrease in volume, and (b) by releasing circulation suddenly after prior arrest and measuring increase in volume during the ensuing mild hyperemia. The term "dynamic vascular volume" was used to indicate that the volume of blood in actual movement was being measured under these conditions.

In the normal forearm "dynamic vascular volumes" were greatest when external pressure was between 15 and 35 mm. Hg, becoming less at external pressures above and below this range.

To record the relation between "dynamic vascular volume" and external pressure in the form of a single numerical value, an objective method of analyzing the pressure-volume curves was adopted. The single value thus obtained was termed Pmvc and was defined as "that external pressure at which the vis a tergo of the circulation is able to keep open the greatest collective dynamic vascular volume."

Pmvc determined in the forearms of 20 normal subjects with the forearm segment at heart level and at 34° C. was 27, 21 and 21 mm. Hg by Methods I, II, and III respectively. Reasons are given for regarding Methods I and II as the most useful. In the normal subject the results by all three methods had roughly the same order of magnitude as average capillary blood pressure when determined directly.

This similarity between Pmvc and directly determined capillary blood pressure held also when the latter was reduced by elevating the forearm or increased by known venous congestion and by depressing the forearm below heart level.

With due precaution against assuming too quickly the quantitative validity of any indirect method of measuring intravascular pressure, it is suggested that the plethysmographic method may be useful in studying the volume of blood and the pressure in the minute vessels of the forearm in clinical conditions.

L. W. Roth.

Leary, T.: Arteriosclerosis. Bull. New York Acad. Med. **17**: 887, 1941.

Atherosclerosis, the important form of arteriosclerosis, is distinguished from other forms of arteriosclerosis by the presence of excess cholesterol in the lesions. It is the "cholesterol disease" of man.

Excess cholesterol, i.e., visible cholesterol, is an irritant, producing lesions in the experimental rabbit (in addition to atherosclerosis) resembling those produced by intravenous silica.

Earliest lesions of atherosclerosis in the experimental rabbit and man are marked by the presence of foam cells containing cholesterol esters in the subendothelial layer of the normal arterial intima. This lesion regresses in atheroma by a mechanism of cholesterol removal. It progresses in atherosclerosis to produce the characteristic nodular lesions of the disease.

In the experimenal rabbit, fed cholesterol, it has been possible to observe the esterification of cholesterol in the liver and the adrenals; deposition of these esters in liver and adrenal cells to the point of becoming a burden; engulfing of the excess esters and their removal from the liver and adrenals by Kupffer and corresponding cells; escape of these cells into the circulation; their passage of the lungs and invasion of the arterial intima. Thus are begun new atherosclerotic lesions, or accretions are made to those already started.

Excess cholesterol is the cause of atherosclerosis. Stresses determine the localization of lesions. Thyroid secretion controls cholesterol metabolism. Sex, age (time + thyroid deterioration) and heredity are modifying factors.

Diet, with limited or absent cholesterol, should prevent atherosclerosis. Vegetable oils, whose sterols are not absorbed, can be substituted for animal fats.

AUTHOR.

Sprague, H. B., and Westinghouse, W.: Arterial Occlusion in Relation to Effort With Special Reference to the Retinal Arteries. New England J. Med. 225: 1002, 1941.

Seventy-seven attacks of acute arterial occlusion in 75 ambulatory patients are described: 30 of these occurred in the retinal arteries of 29 patients, and 47 occurred in other peripheral arteries of 46 patients.

In 3 cases, the occlusion took place during rather severe effort, and in 2, a few minutes after unusual exertion; in 37, the occlusion occurred coincident with mild or very moderate effort, and in 35, when the patient was at rest either in bed or sitting in a chair.

Peripheral arterial occlusion from embolism, thrombosis, or endarteritis rarely occurs during unusual physical effort even in patients with cardiovascular disease of a degree compatible with quite strenuous exertion. In this series, such occlusion occurred approximately fourteen times as often when the patient was at complete rest as when engaged in the ordinary exertions of his usual life.

In approximately half the entire series of arterial occlusion—embolic and obliterative—the patient was physically inactive. This suggests that the conditions necessary for either embolism or thrombosis are as effective with reduced as with increased blood flow, and that the occurrence of such an accident is at least fortuitous.

AUTHOR.

Binford, C. H.: Syphilitic Aneurysm of the Superior Mesenteric Artery. Arch. Path. 33: 691, 1942.

A Negro man, aged 60, presented at autopsy a large syphilitic aneurysm of the superior mesenteric artery and hepar lobatum. The Kahn reaction of the blood was positive, and *Spirochaeta pallida* was demonstrated in sections of the aneurysmal wall.

AUTHOR.

Williams, R. R., and Zeek, P.: Periarteritis Nodosa With Peripheral Polyneuritis and Hyperglycemia: A Case Record Presenting Clinical Problems. Ohio State M. J. 38: 148, 1942.

In this case the diffuse pancreatic involvement accounted for the glycosuria, hyperglycemia, and terminal peritonitis. Either the pancreatitis or the gastric ulcers furnish ample cause for the abdominal pain and vomiting. Lesions also were found which accounted for the testicular tenderness and the polyneuritis. The partial plugging of the ampulla of Vater may have caused the jaundice. The widespread involvement of the blood vessels, both in the kidneys and elsewhere, was probably the basis for the hypertension and myocardial hypertrophy.

The correct diagnosis in this case was made clinically on the basis of a generalized systemic febrile disease with manifestation referable to multiple viscera, hypertension, and progressive peripheral polyneuritis. The muscles taken for biopsy did not contain small arteries of the type usually involved in periarteritis nodosa and was therefore of no value in diagnosis. The skin biopsy, however, contained a small artery and confirmed the clinical impression. It is of interest that this positive biopsy was obtained from the area of the papulo-vesicular dermatitis over the abdomen.

AUTHORS.

Master, A. M., Dack, S., and Jaffe, H. L.: Follow-Up Studies in Coronary Occlusion. I. Degree of Recovery, Symptoms, and Physical Signs. New York State J. Med. 42: 413, 1942.

A detailed follow-up study of the cardiac status, as determined by symptoms and physical examination, has been made in a group of 202 patients who had recovered from an acute coronary occlusion one to six years previously.

Clinical recovery from the attack was good in one-third, poor in two-fifths, and fair in the remainder of the series. Two-fifths showed no or only slight restriction of physical activity.

Two-thirds of the patients complained of precordial pain, dyspnea, or fatigue and one-third had no symptoms of cardiac disability.

Angina pectoris occurred in three-fifths of the patients. Coronary occlusion may initiate an anginal syndrome or aggravate one previously present. On the other hand, pre-existing angina pectoris may disappear completely following the attack. The presence or absence of anginal pectoris was not influenced by the level of the blood pressure.

Dyspnea, present in over half the patients, was occasionally the only symptoms of heart failure or cardiac disability.

Weakness was common but only rarely occurred in the absence of pain or dyspnea.

Chronic congestive heart failure was present in one-fourth the patients, a much lower incidence than during the attack and of a milder degree.

Persistent diminished amplitude of the heart sounds, particularly the first apical sound, was observed in about one-half the patients. This sign may be of diagnostic value in subjects over 40 suspected of coronary disease. Gallop rhythm, a sign of a failing heart, was not uncommon.

The heart rate and rhythm were normal in the great majority of patients. Paroxysmal or permanent auricular fibrillation occurred in only 5 patients. The rarity of arrhythmias in this series is in marked contrast to their frequency in the acute stage of coronary occlusion.

Hypertension, which had been present in two-thirds of the patients prior to the acute attack, returned or persisted in only one-third of the group following recovery. Although hypertension did not influence the frequency or severity of angina pectoris or the frequency of subsequent attacks, it was more common in those who developed heart failure and in those whose clinical recovery was poor.

One-half of the patients resumed their former occupations, either full or part time. Inability to work was nearly always attributable to an anginal syndrome or heart failure. Mild angina pectoris or dyspnea, however, did not prevent return to work. The great majority of patients who resumed work did so within six months after discharge from the hospital.

It is concluded that at least one-third of hospital ward patients who recover from acute coronary occlusion may lead a fairly active life with no, or only slight, restriction of ordinary activities.

AUTHORS.

Reitman, N., Greenwood, W. R., and Kler, J. H.: Coronary Thrombosis in a Young Diabetic. Am. J. M. Sc. 203: 792, 1942.

A case of coronary thrombosis in a diabetic youth of 20 years is presented.

The relationship of cholesterol metabolism to diabetes and the premature onset of coronary disease is briefly discussed.

AUTHORS.

Espersen, T.: Studies on the Cardiac Output and Related Circulatory Functions, Especially in Patients With Congestive Heart Failure. Acta med. Scandinav. **108**: 153, 1941.

A brief review is given of the results reported by some previous investigators in determination of the cardiac output in the clinic, especially on cardiac patients. It is pointed out that in most instances the technique has been of dubious value. In particular, in determinations carried out on cardiac patients presenting phenomena of incompensation, only minor significance has been attributable to a majority of the reported results because they were obtained with anything but a reliable technique and, hence, seemed too accidental.

The writer, therefore, has given an account of the results of his own circulatory studies. To all his experimental subjects, he has applied the method given originally by Ejnar Nielsen, and later modified by the writer. In addition, Grollman's rebreathing procedure (modified) has been employed too in a good many of these cases.

It is shown that the values obtained for oxygen utilization and thus for the cardiac output and stroke volume too in determinations on heart and lung normal subjects (Group I) after the Nielsen method are of the same magnitude as those obtained by determination after Grollman.

In 16 patients with compensated cardiac disease (Group II) the values obtained for the cardiac index after the Nielsen method were of normal magnitude in 14 cases; in the remaining two cases the values were just about at the lower normal limit.

In nine of these 16 patients it proved practicable to carry through experiments with the modification of the Grollman method suggested by Grollman, Friedman, Clark and Harrison. The results agree fairly well with those obtained after the Nielsen method.

In the compensated cardiac patients, the values obtained for the oxygen utilization are about 8 per cent (Nielsen method) and 6 per cent (Grollman method) higher than the values obtained in the normal material after the same methods—in other words, they are of the same magnitude as the average values for utilization in persons with normal circulation. But the variability of the obtained values is greater in Group II than in Group I.

Among the 27 patients with incompensated cardiac disease (Group III) examined after the Nielsen method, 15 showed a cardiac index of normal magnitude (in one case, at the upper normal limit), whereas the cardiac output was found to be decreased in the remaining 12 cases.

The average utilization for the entire Group III is respectively 35 per cent and 25 per cent higher than the corresponding values for Group I and Group II. In Group III the variability of the values for oxygen utilization is considerably greater than in the first two groups.

In 16 of the 27 patients of Group III the oxygen utilization was found to be higher than normal; in the remaining 11 cases the utilization values were of normal magnitude.

Among 12 patients with more or less pronounced cyanosis 4 showed normal oxygen utilization and normal cardiac output.

Albuminuria was present in ten of the patients in Group III. In five of these cases the cardiac output was found to be decreased; in the remaining five the cardiac output was normal.

For examination of incompensated cardiac patients the Nielsen method is superior to the Grollman method and its modifications, not only theoretically but also technically. Among the 23 of the 27 patients in Group III on whom the writer tried to carry out the Grollman determination, only 13 were able to perform the breathing

technique in a fairly serviceable degree. In 9 of these cases the results obtained after the two methods agreed fairly well.

The experimental results here presented go against the forward-failure hypothesis. Theories based on "back-pressure" are compatible with the experimental results here reported.

AUTHOR.

Lilienfeld, A., and Berliner, K.: Duplicate Measurements of Circulation Time Made With the Alpha Lobeline Method. Arch. Int. Med. **69**: 739, 1942.

One hundred duplicate measurements of circulation time were made, with alpha lobeline hydrochloride used as an agent. The interval between tests varied from fifteen to sixty minutes.

Considerable differences in the results of the duplicate tests were observed in many instances. In only 3 cases were identical results obtained. In 85 cases the differences varied from 3 to 199 per cent, with an average variation of 29 per cent. The result of the second test was higher than that of the first just as frequently as it was lower. In 12 cases the second injection failed altogether to produce cough.

The factors which may have been responsible for the variations in results are discussed.

Differences in the results of duplicate tests were greatest in patients suffering from congestive heart failure. Other investigators using different methods reported the same observation. Tests of circulation time in general and the alpha lobeline test in particular should not be relied upon to evaluate the progress of a patient with congestive heart failure unless the changes shown by these tests are marked.

AUTHORS.

Wiggers, C. J., and Werle, Jacob M.: Cardiac and Peripheral Resistance Factors Determinants of Circulatory Failure in Hemorrhagic Shock. Am. J. Physiol. **136**: 421, 1942.

Dogs under morphine-barbital were bled until a marked state of hypotension was maintained for several hours. At the end of such a period the withdrawn blood (heparinized) was reinjected. A state of shock was considered to exist when such reinfusion failed to maintain arterial pressures for at least three hours and the upper intestines showed hemorrhagic changes at autopsy.

Cardiometer curves were recorded optically with aortic and venous pressures, and simultaneously on a kymograph as well. Changes in cardiac behavior were assessed from critically evaluated optical volume curves. Total peripheral resistance (TPR) was calculated from $\frac{\text{mean pressure} \times 1332}{\text{cardiac output/sec.}}$ by use of calibrated drum records.

Experiments on 11 dogs consistently showed decreases in stroke and minute volumes during post-hemorrhagic hypotension and postinfusion failure, but the manner in which such reduction was occasioned differed. In one group, decrease in stroke was accompanied by decreasing venous pressures, in another it developed despite an elevation. Analyses of volume curves indicate that the capacity of the ventricles to respond to a given venous pressure (stretch) is reduced and that such hypodynamic action is masked when venous pressures decline concurrently. Prolonged reduction in coronary flow during severe hypotension is suggested as the cause. Our results strongly suggest that reduced capacity of the myocardium to respond to given venous pressures is one of the factors which precipitates an irreversible circulatory state.

In the majority of animals TPR increased during the period of posthemorrhagic hypotension as well as after infusion, regardless of whether irreversible failure supervened or not. Such increase was never maximal, for stimulation of pressor nerves temporarily increased TPR tremendously. Dogs that showed little recovery of arterial pressure after initial hemorrhage, and some of those that developed rapid circulatory

failure after reinfusion showed no increase in TPR. Consequently, our conclusion that development of hemorrhagic shock is not contingent on existence of high or low TPR. Persistence of an augmented TPR seems to retard rather than facilitate the development of hemorrhagic shock. Failure of a compensatory increase in TPR may be a second precipitating factor in creation of an irreversible state.

L. W. ROTH.

Burch, G. E., Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip, and Posteriosuperior Portion of the Pinna of Resting Normal White Adults. Am. J. Physiol. **136**: 433, 1942.

The spontaneous variations in volume of the tip of the right index finger, the tip of the right second toe and the posterosuperior portion of the right pinna of 12 normal white adults have been studied quantitatively. All parts have undergone continuous variations in blood volume which consist of at least five separate rhythms. The effects of the heartbeat and respiration were reflected in the pulse waves and respiratory waves respectively. The three other waves were arbitrarily named alpha, beta, and gamma.

The mean frequency of the alpha waves was 7.9 per minute in the finger tip, 7.7 in the toe tip, and 8.6 in the pinna. The mean volume of the deflections was 14.5 cu. mm. per 5 c.c. of finger, 7.1 cu. mm. per 5 c.c. of toe and 6.6 cu. mm. per 5 c.c. of pinna. The frequency of the beta deflections varied from one to two per minute and the size from 5 to 60 cu. mm. per 5 c.c. of tissue. The number of gamma deflections varied from one to eight per hour and the volume from 50 to 350 cu. mm. per 5 c.c. of tissue.

The alpha waves obtained from the finger tips of the 12 subjects fell into three types. In type I (5 subjects) the deflections were relatively small and varied very little in size. Type III (6 subjects), on the other hand, showed a wide spread in the sizes of the deflections, many being large. Type II waves, found in a single subject, were intermediate between those of type I and type III. The subjects with type I were phlegmatic and stable while those with type III were excitable and exhibited wide fluctuations in mood.

L. W. ROTH.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Tips of the Fingers and Toes and Posterosuperior Portion of the Pinna of Hypertensive Patients and Senile Subjects. Am. J. Physiol. **136**: 451, 1942.

The spontaneous variations in volume of the peripheral blood vessels of the tip of the right index finger, the tip of the right second toe, and the posterosuperior portion of the right pinna were found to be about the same in patients with diencephalic hypertension as in those with renal hypertension. The configurations and other characteristics of the 5 types of rhythm in the blood vessels of these parts were found to be essentially the same as those described as occurring in normal subjects. In no instance were the alpha waves of these patients of type I. Of the 13 patients with hypertension, 10 exhibited type II waves, and 3, type III. All were emotionally unstable and excitable.

In senile subjects the 5 types of rhythmic spontaneous variations were also about the same as in the normal subjects and in the patients with hypertension, with the exception of the volume of the pulse waves of the toes which was smaller. Such small waves are probably due in large part to arteriosclerotic changes. The alpha waves in all of the senile subjects were of the stable variety, type I. Whether this is due to a sluggish psychosomatic state so well known in senile individuals and also whether individuals who are emotionally stable and not easily excitable live longer is a problem which was not studied.

L. W. ROTH.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study of the Relationship Between the Pulse and Alpha Waves of the Tips of the Fingers and Toes of Five Adults. Am. J. Physiol. **136**: 448, 1942.

Simultaneous alpha deflections and pulse waves in the finger tips were concordant in 34 per cent, and in the toe tips in 71 per cent. The range was 22 to 50 per cent in the finger tips and 62 to 76 per cent in the toe tips. In the finger and toe tips simultaneous alpha waves were concordant in 56 per cent, the range being 50 to 62. The pulse waves were concordant in 45 per cent. Forty-five per cent of the simultaneous variations in the size of the pulse waves in the finger and toe tips were concordant.

AUTHORS.

Wood, E. H., and Moe, G. K.: The Measurement of Edema in the Heart-Lung Preparation. Am. J. Physiol. **136**: 506, 1942.

The average ventricular weight/body weight, and lung weight/body weight ratios from eighty-five heart-lung preparations have been compared with similar ratios from normal dogs. The differences found in the average ratios indicate that on the average 18 per cent and 60 per cent of the final heart-lung ventricular and lung weights respectively are edema fluid.

Satisfactory agreement was found between the edema calculated from cardiac chloride analyses and the edema determined by the weight increase of four blood-perfused Langendorff dog hearts.

The average ventricle weight/body weight ratios of 23 heart-lung hearts corrected for edema on the basis of chloride analyses was not significantly different from normal.

The edema content of heart-lung hearts cannot be adequately corrected for edema on the basis of tissue water content. Concentrations of tissue constituents of this or similar preparations are of little significance if expressed on a dry or a wet weight basis.

In the majority of heart-lung preparations a positive correlation exists between the relative magnitudes of cardiac and lung edema which occurs. This constitutes an indication that similar factors are responsible for the edema formation in the two organs.

The major part of the edema fluid which accumulates in heart-lung hearts appears to be extracellular in position.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: The Vasomotor Components in the Vascular Reactions in the Finger to Cold. Am. J. Physiol. **136**: 669, 1942.

The vascular reactions in the finger to chilling have been examined by means of the photoelectric plethysmograph. Analysis of these reactions was concerned with the role of the vasomotor reflexes.

The initial immediate constriction on application of cold is due to vasoconstrictor reflexes on which is superimposed somewhat later the direct constrictor action of cold. Evidence:

1. Accompanying constriction occurs also in the warm control fingers of the same and opposite hands, but the constriction is usually more intense in the chilled finger.

2. If a vasoconstrictor reflex is not elicited in the control fingers by an application of moderate cold, the constriction in the chilled finger occurs in a gradual progressive manner, as in the forehead skin, due to the direct constrictor effect of cold on the vessels.

The reactive dilatation which follows in the chilled finger within three to eight minutes after the application of cold, occurs independently of the vasomotor system.

Evidence:

1. The dilatation may be limited to the chilled finger and may occur there when the vasoconstrictor tone is high in the control fingers.

2. Vasoconstrictor reflexes were elicited in the chilled finger during the reactive dilatation in some experiments, while in other instances definite evidence of vasoconstrictor paralysis in the chilled finger was obtained.

L. W. Roth.

Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation. M. Clin. North America **26**: 943, 1942.

The presence of fluorescein in the tissue can be easily determined by its fluorescence under filtered ultraviolet light of a certain wavelength. This method which was first published by one of the authors in 1931 for directly and objectively determining the circulation time can also be used for establishing the presence or adequacy of local circulation. In regard to the first it is an objective method devoid of the defects of other procedures, in respect to the second it seems to possess greater delicacy and wider utility than the injection of radiopaque whose field of application is naturally rather limited.

The new objective method for determining the circulation time yields the following values: Normal adults range from 15 to 20 seconds with an average of 17.1 seconds in eighty-nine patients from arm to lips, in cardiac failure the time varies from 20 to 68 seconds (average 39) although 10 per cent of seventy-eight patients had a normal reading; hyperthyroidism was always associated with a shortened circulation time, 7 to 14 seconds (average 10.6 seconds in thirty-six cases). Neither Lugol's solution nor operation immediately induce a reversion to normal, despite a favorable influence on the basal metabolic rate by these measures. Eight of nine cases of hypothyroidism showed a prolonged circulation time of 21 to 34 seconds (average 26 seconds).

Although the dye can be used to determine the circulation time in all types of experimental animals without recourse to anesthesia and hence permits studies of the permeability of vessels under the influence of drugs, this has not been discussed at any length in this clinical paper.

The intestine of experimental animals and man shows an intense fluorescence after the intravenous injection of fluorescein and ultraviolet illumination of the intestine. Incarcerated portions of the bowel do not give this emission; the adequacy of the blood supply to the viscus, after liberation from incarceration, can be immediately ascertained. Clamping of the mesenteric arteries may cause infarction which can be demonstrated by the absence of fluorescence in the area affected. The importance of these observations hardly requires emphasis.

Finally the skin can also be made fluorescent; the portions of the extremities not supplied by blood remain dark rather than fluorescent. The application of this diagnostic aid in peripheral vascular disease has been shown by an illustrative case of diabetic gangrene; inadequate blood supply is shown by diminished fluorescence.

Authors.

Hertzman, A. B., and Roth, L. W.: The Reactions of the Digital Artery and Minute Pad Arteries to Local Cold. Am. J. Physiol. **136**: 680, 1942.

A. The selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger were demonstrated by means of photoelectric plethysmographs.

The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold. Its later constriction during the continued application of cold appears to be due to the direct effects of the fall in temperature on the artery.

The reactive dilatation which appears during the application of cold is limited to the minute pad vessels and does not involve the digital artery until the resultant rise in finger temperature permits relaxation of this artery.

B. The effects of these reactions on the propagation of the pulse in the finger's arterial system were studied by recording the pad pulses with high frequency galvanometers.

In the usual experiment, the time relations and form of the pad pulses in the chilled finger were altered only moderately and in the direction which could be predicted from the relative participation of the pad and digital arteries in the reactions to cold.

In a few normal subjects, the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension, thus suggesting that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arterio-venous communications.

L. W. ROTH.

Montgomery, H.: The Effect of Drugs on the Circulation in Normal Hands and Feet. Am. J. M. Sc. **203**: 882, 1942.

Measurements of digital blood flow were made in normal subjects given vasodilator drugs. Consideration was given to the normal factors influencing blood flow, i.e., food, environmental temperature, and exercise. The approximate effectiveness of various normal and operative procedures and drugs intended to increase peripheral blood flow are indicated.

A study of the influence of several promising drugs and other factors upon digital blood flow in normal subjects shows that digital blood flow is augmented by these agents in the following order of intensity: (1) heat to the body sufficient to raise the body temperature slightly; (2) alcohol by mouth, such as whisky in doses of 2 to 6 ounces; (3) food; (4) papaverine intravenously; and (5) mecholyl by mouth. The approximated optimum doses and routes of the drugs are given.

Certain powerful vasodilator drugs decrease peripheral blood flow, probably because they have selective vasodilator action elsewhere or because they induce peripheral vasoconstriction by the carotid sinus reflex: amyl nitrite by inhalation, mecholyl (12 mg.), and doryl by hypodermic (0.5 mg.). In these instances the blood pressure falls.

AUTHOR.

Boyer, N. H., and White, P. D.: Right-Upper-Quadrant Pain on Effort: An Early Symptom of Failure of the Right Ventricle. New England J. Med. **226**: 217, 1942.

We have recently encountered 4 patients in whom right-upper-quadrant pain, precipitated by exertion and relieved by rest, has been the presenting symptom of early right-sided heart failure. It is evidently due to acute congestion of the liver and is comparable to dyspnea on effort in early left-sided heart failure.

Direct questioning of a group of 40 patients who already had clinically evident right-sided failure, or were likely candidates for it, revealed that the pain had been present at some time in about 45 per cent. It is a symptom to which the patient rarely attaches much significance, since it is usually of little severity and is overshadowed by more uncomfortable symptoms.

If the symptom is sought as diligently as the history of dyspnea on exercise, it may be found to be a fairly common and reliable warning of weakness of the right ventricle.

AUTHORS.

Book Review

DER MYOKARD INFARKT. ERKENNUNG, BEHANDLUNG UND VERHÜTUNG, BD.I OF KREISLAUFBÜCHERER (DEUTSCHE GESELLSCHAFT FÜR KREISLAUFFORSCHUNG): By Max Hochrein. Theo. Steinkopff, Dresden u. Leipzig, 1941, second edition, 278 pages, 58 illustrations.

This book brings before the American cardiologist the views of one of his best informed German colleagues. It cannot be recommended for the graduate student, for it fails to include many important recent contributions, and it accepts many points which are not generally accepted in this country. It clearly shows how quickly the chasm produced by the war has made itself felt, and also how rapidly our knowledge in this field is growing. In some respects the book is already obsolete.

A brief but comprehensive historical review is followed by a discussion of the incidence of myocardial infarction and a good description of the anatomy and innervation of the coronary arteries and their normal physiology. In this field, the author has made notable contributions. He takes issue with Anrep, who states that systole acts as an impediment to the coronary circulation. He also discusses the lung as a physiological blood depot and reviews experimental coronary occlusion.

The description of the pathological anatomy does not include the recently discovered prodromal changes which occur in the wall of the artery and which are of fundamental importance for our understanding of the whole problem.

The remaining three-quarters of the book contain the clinical aspects of the subject. The author places great emphasis on spasm as an immediate cause of coronary occlusion. He attributes this to a constitutional disturbance of the vegetative balance. As secondary causes he accepts focal infection (though without conclusive evidence), nicotine, coffee, and excitement. The part played by effort is uncertain. Although he quotes Master, Dack, and Jeffe's analysis of activities associated with the onset of acute coronary occlusion he ignores their conclusions in his discussion. Among his patients, the coincidence of diabetes and coronary occlusion is not increased.

Hochrein concludes that myocardial infarction does not always result from coronary sclerosis and thrombosis, but often from a functional disturbance of the coronary circulation.

There follows a discourse on the medicolegal aspects of myocardial infarction. Extraneous factors, e.g., excitement and sudden effort, are accepted as causing myocardial infarction. While the author duly distinguishes between predisposing and precipitating factors, he further distinguishes between such precipitating factors as are peculiar to the patient's occupation, and such as accidentally happen while the patient is at work, e.g., climbing stairs or running to catch a streetcar. Compensation is not awarded in these cases. This section should be read by all interested in forensic cardiology.

In the symptomatology the classical picture is sharply drawn and so are many atypical ones. The author states (p. 202) that at the time the book was written no studies had been published throwing light on the prodromal symptoms which are so important in studying the pathogenesis of myocardial infarction. The chest leads have not been given the attention which we believe they deserve, nor is the time relationship between the symptoms and the electrocardiographic changes fully discussed.

Hochrein attributes the constitutional changes (hypoglycemia, increased sedimentation rate, etc.) to a secretory insufficiency resulting from insufficient circulation. He attributes the early leucocytosis to dyspnea. The references which he has collected should prove valuable to anyone studying the secretion and metabolic aspects of myocardial infarction.

In discussing the diagnosis, no clear distinction is made between long-lasting precordial pain not followed by evidence of myocardial infarction (here called angina pectoris), and that caused by infarction. He distinguishes between angina pectoris vera, angina pectoris vasomotorica, and acute and gradual myocardial infarction. The electrocardiagraphic differentiation between "posterior myocardial infarction" and "pulmonary infarction" and between pericarditis, acute abdominal conditions, and myocardial infarction is not fully described, but the discussion of the localization of the infarcted area is excellent.

Hochrein attributes the recently improved prognosis to better treatment. However, he does not show that the death rates, which he compares, come from comparable groups. Groups from the receiving rooms of city hospitals, from their wards, and from a cardiologist's private office are not comparable. The inclusion of lighter cases resulting from better recognition of the condition in recent years has caused a lowering of the recorded death rate which Hochrein has not sufficiently discounted. While we now give myocardial infarction a better prognosis than we formerly did, at least much of the improvement is attributable to improved knowledge rather than to improved treatment.

Discussing the treatment, the author emphasizes the value of "natural rest," and to rest the gastrointestinal tract he prescribes an excellent diet, but he supports this treatment with a long list of drugs with fancy names and hypothetical effects. However, in his stand on the use of digitalis he is very close to the best Anglo-Saxon principles, in contrast to the divergent views of Edens and his group.

In a final prophylactic chapter, Hochrein discusses means of improving the coronary circulation, baths, electric treatment, elimination of foci of infection, graduated exercises, and many others. He is fully aware of the rather hypothetical value of all of them. He ends his book by stating that the main problem of myocardial infarction is one of recognizing the manner of its evolution, for only thus can we hope to prevent it.

JULIUS JENSEN.

With deep regret we announce the death of Doctor Charles Virgil Mosby, Chairman of the Board of The C. V. Mosby Company, St. Louis, Missouri.

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For the Study of the Circulation

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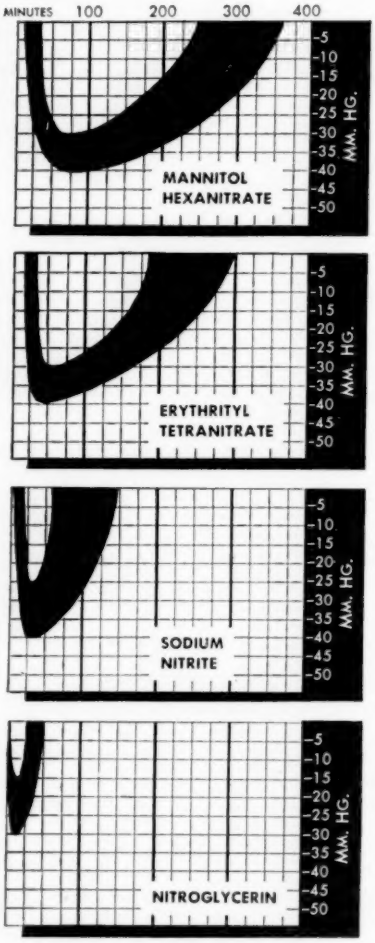

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